

MACROCYCLIC COMPOUNDS AND METHODS OF MAKING AND USING THE SAME

RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Patent Application No. 60/548,280, filed February 27, 2004, and to U.S. Patent Application No. 60/575,949, filed June 1, 2004, the entire disclosures of each of which are incorporated by reference herein.

5 FIELD OF THE INVENTION

The present invention relates generally to the field of anti-infective, anti-proliferative, anti-inflammatory, and prokinetic agents. More particularly, the invention relates to a family of macrocyclic compounds that are useful as such agents.

BACKGROUND

10 Since the discovery of penicillin in the 1920s and streptomycin in the 1940s, many new compounds have been discovered or specifically designed for use as antibiotic agents. It was once believed that infectious diseases could be completely controlled or eradicated with the use of such therapeutic agents. However, such beliefs have been shaken because strains of cells or microorganisms resistant to currently effective therapeutic agents continue to evolve. In fact,
15 virtually every antibiotic agent developed for clinical use has ultimately encountered problems with the emergence of resistant bacteria. For example, resistant strains of Gram-positive bacteria such as methicillin-resistant staphylococci, penicillin-resistant streptococci, and vancomycin-resistant enterococci have developed. These resistant bacteria can cause serious and even fatal results for patients infected with such resistant bacteria. Bacteria that are resistant to macrolide
20 antibiotics have emerged. Also, resistant strains of Gram-negative bacteria such as *H. influenzae* and *M. catarrhalis* have been identified. See, e.g., F.D. Lowry, "Antimicrobial Resistance: The Example of *Staphylococcus aureus*," *J. Clin. Invest.*, vol. 111, no. 9, pp. 1265-1273 (2003); and Gold, H.S. and Moellering, R.C., Jr., "Antimicrobial-Drug Resistance," *N. Engl. J. Med.*, vol. 335, pp. 1445-53 (1996).

25 The problem of resistance is not limited to the area of anti-infective agents, because resistance has also been encountered with anti-proliferative agents used in cancer chemotherapy.

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Therefore, the need exists for new anti-infective and anti-proliferative agents that are both effective against resistant bacteria and resistant strains of cancer cells.

Despite the problem of increasing antibiotic resistance, no new major classes of antibiotics have been developed for clinical use since the approval in the United States in 2000 of the oxazolidinone ring-containing antibiotic, linezolid, which is sold under the tradename Zyvox[®]. See, R.C. Moellering, Jr., "Linezolid: The First Oxazolidinone Antimicrobial," *Annals of Internal Medicine*, vol. 138, no. 2, pp. 135-142 (2003). Linezolid was approved for use as an anti-bacterial agent active against Gram-positive organisms. However, linezolid-resistant strains of organisms are already being reported. See, Tsiodras *et al.*, *Lancet*, vol. 358, p. 207 (2001); Gonzales *et al.*, *Lancet*, vol 357, p. 1179 (2001); Zurenko *et al.*, *Proceedings Of The 39th Annual Interscience Conference On Antibacterial Agents And Chemotherapy (ICAAC)*, San Francisco, CA, USA (September 26-29, 1999).

Another class of antibiotics is the macrolides, so named for their characteristic 14- to 16-membered ring. The macrolides also often have one or more 6-membered sugar-derived rings attached to the main macrolide ring. The first macrolide antibiotic to be developed was erythromycin, which was isolated from a soil sample from the Philippines in 1952. Even though erythromycin has been one of the most widely prescribed antibiotics, its disadvantages are relatively low bioavailability, gastrointestinal side effects, and a limited spectrum of activity. Another macrolide is the compound, azithromycin, which is an azolide derivative of erythromycin incorporating a methyl-substituted nitrogen in the macrolide ring. Azithromycin is sold under the tradename Zithromax[®]. A more recently introduced macrolide is telithromycin, which is sold under the tradename Ketek[®]. Telithromycin is a semisynthetic macrolide in which a hydroxyl group of the macrolide ring has been oxidized to a ketone group. See Yong-Ji Wu, Highlights of Semi-synthetic Developments from Erythromycin A, *Current Pharm. Design*, vol. 6, pp. 181-223 (2000), and Yong-Ji Wu and Wei-uo Su, Recent Developments on Ketolides and Macrolides, *Curr. Med. Chem.*, vol. 8, no. 14, pp. 1727-1758 (2001).

In the search for new therapeutic agents, researchers have tried combining or linking various portions of antibiotic molecules to create multifunctional or hybrid compounds. Other researches have tried making macrolide derivatives by adding further substituents to the large macrolide ring or associated sugar rings. However, this approach for making macrolide derivatives has also met with limited success.

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Notwithstanding the foregoing, there is an ongoing need for new anti-infective and anti-proliferative agents. Furthermore, because many anti-infective and anti-proliferative agents have utility as anti-inflammatory agents and prokinetic agents, there is also an ongoing need for new compounds useful as anti-inflammatory and prokinetic agents. The present invention provides

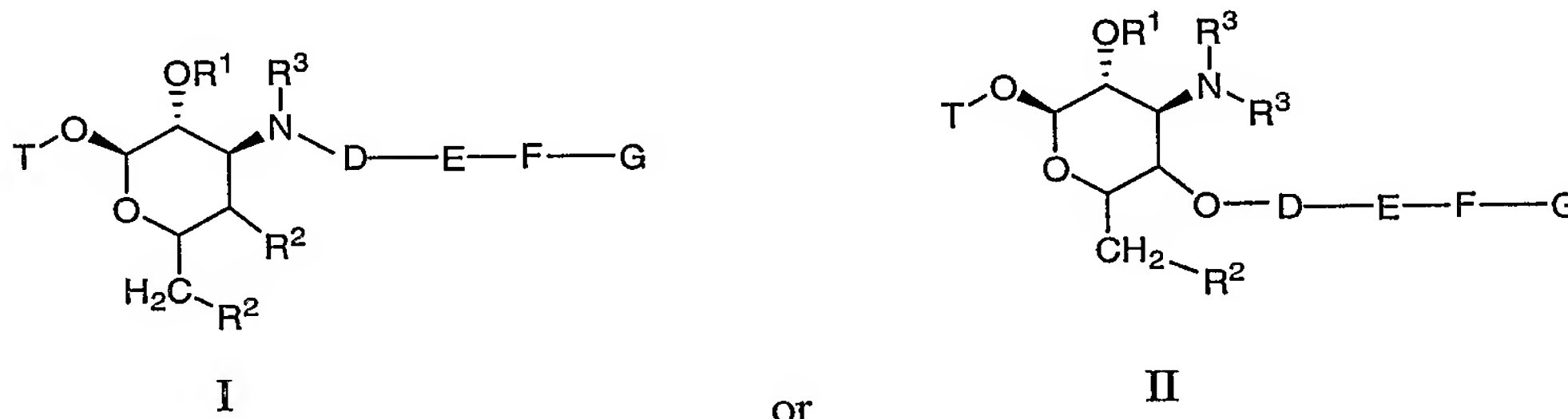
5 compounds that meet these needs.

SUMMARY OF THE INVENTION

The invention provides compounds useful as anti-infective agents and/or anti-proliferative agents, for example, anti-biotic agents, anti-microbial agents, anti-bacterial agents, anti-fungal agents, anti-parasitic agents, anti-viral agents, and chemotherapeutic agents. The

10 present invention also provides compounds useful as anti-inflammatory agents, and/or prokinetic (gastrointestinal modulatory) agents. The present invention also provides pharmaceutically acceptable salts, esters, *N*-oxides, or prodrugs thereof.

The present invention provides compounds having the structure of formula I or II:



15 or a stereoisomer, pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof. In the formula, variables T, D, E, F, G, R¹, R², and R³, can be selected from the respective groups of chemical moieties later defined in the detailed description.

In addition, the invention provides methods of synthesizing the foregoing compounds. Following synthesis, a therapeutically effective amount of one or more of the compounds may be

20 formulated with a pharmaceutically acceptable carrier for administration to a mammal, particularly humans, for use as an anti-cancer, anti-biotic, anti-microbial, anti-bacterial, anti-fungal, anti-parasitic or anti-viral agent, or to treat a proliferative disease, an inflammatory disease or a gastrointestinal motility disorder, or to suppress disease states or conditions caused or mediated by nonsense or missense mutations. Accordingly, the compounds or the

25 formulations may be administered, for example, via oral, parenteral, or topical routes, to provide an effective amount of the compound to the mammal.

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The foregoing and other aspects and embodiments of the invention may be more fully understood by reference to the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

5 The present invention provides a family of compounds that can be used as anti-proliferative agents and/or anti-infective agents. The compounds may be used without limitation, for example, as anti-cancer, anti-microbial, anti-bacterial, anti-fungal, anti-parasitic and/or anti-viral agents. Further, the present invention provides a family of compounds that can be used without limitation as anti-inflammatory agents, for example, for use in treating chronic
10 inflammatory airway diseases, and/or as prokinetic agents, for example, for use in treating gastrointestinal motility disorders such as gastroesophageal reflux disease, gastroparesis (diabetic and post surgical), irritable bowel syndrome, and constipation. Further, the compounds can be used to treat or prevent a disease state in a mammal caused or mediated by a nonsense or missense mutation.

15 The compounds described herein may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the
20 compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separate isomeric forms. All chiral, diastereomeric, racemic, and geometric isomeric forms of a structure are intended, unless specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare
25 compounds of the present invention and intermediates made therein are considered to be part of the present invention. All tautomers of shown or described compounds are also considered to be part of the present invention.

1. Definitions

30 The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the

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designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N).

5 The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

10 When any variable (e.g., R³) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with one or more R³ moieties, then the group may optionally be substituted with one, two, three, four, five, or more R³ moieties, and R³ at each occurrence is selected independently from the definition of R³. Also, combinations of substituents and/or variables are permissible, but only if such combinations
15 result in stable compounds.

A chemical structure showing a dotted line representation for a chemical bond indicates that the bond is optionally present. For example, a dotted line drawn next to a solid single bond indicates that the bond can be either a single bond or a double bond.

20 When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible, but only if such combinations
25 result in stable compounds.

In cases wherein there are nitrogens in the compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of the present invention. Thus, all shown and claimed nitrogens are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

As used herein, the term "anomeric carbon" means the acetal carbon of a glycoside.

30 As used herein, the term "glycoside" is a cyclic acetal.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C₁₋₆ alkyl is

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intended to include C₁, C₂, C₃, C₄, C₅, and C₆ alkyl groups. C₁₋₈ alkyl is intended to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, and C₈ alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, n-hexyl, n-heptyl, and n-octyl.

5 As used herein, "alkenyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more unsaturated carbon-carbon bonds that may occur in any stable point along the chain, such as ethenyl and propenyl. C₂₋₆ alkenyl is intended to include C₂, C₃, C₄, C₅, and C₆ alkenyl groups. C₂₋₈ alkenyl is intended to include C₂, C₃, C₄, C₅, C₆, C₇, and C₈ alkenyl groups.

10 As used herein, "alkynyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more triple carbon-carbon bonds that may occur in any stable point along the chain, such as ethynyl and propynyl. C₂₋₆ alkynyl is intended to include C₂, C₃, C₄, C₅, and C₆ alkynyl groups. C₂₋₈ alkynyl is intended to include C₂, C₃, C₄, C₅, C₆, C₇, and C₈ alkynyl groups.

15 Furthermore, "alkyl", "alkenyl", and "alkynyl" are intended to include moieties which are diradicals, i.e., having two points of attachment, an example of which in the present invention is when D is selected from these chemical groups. A nonlimiting example of such an alkyl moiety that is a diradical is -CH₂CH₂-, i.e., a C₂ alkyl group that is covalently bonded via each terminal carbon atom to the remainder of the molecule.

20 As used herein, the terms used to describe various carbon-containing moieties, including, for example, "alkyl," "alkenyl," "alkynyl," "phenyl," and any variations thereof, are intended to include univalent, bivalent, or multivalent species. For example, "C₁₋₆ alkyl-R³" is intended to represent a univalent C₁₋₆ alkyl group substituted with a R³ group, and "O-C₁₋₆ alkyl-R³" is intended to represent a bivalent C₁₋₆ alkyl group, i.e., an "alkylene" group, substituted with an
25 oxygen atom and a R³ group.

 As used herein, "cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C₃₋₈ cycloalkyl is intended to include C₃, C₄, C₅, C₆, C₇, and C₈ cycloalkyl groups.

 As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo.

30 "Counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

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As used herein, "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where $v = 1$ to 3 and $w = 1$ to $(2v+1)$). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl.

As used herein, "alkoxy" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-6} alkoxy, is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , and C_6 alkoxy groups. C_{1-8} alkoxy, is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , and C_8 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, s-pentoxy, n-heptoxy, and n-octoxy.

As used herein, "alkylthio" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through a sulfur bridge. C_{1-6} alkylthio, is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , and C_6 alkylthio groups. C_{1-8} alkylthio, is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , and C_8 alkylthio groups.

As used herein, "carbocycle" or "carbocyclic ring" is intended to mean, unless otherwise specified, any stable 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12-membered monocyclic, bicyclic or tricyclic ring, any of which may be saturated, unsaturated, or aromatic, recognizing that rings with certain numbers of members cannot be bicyclic or tricyclic, e.g., a 3-membered ring can only be a monocyclic ring. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl. As shown above, bridged rings are also included in the definition of carbocycle (e.g., [2.2.2]bicyclooctane). A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Fused (e.g., naphthyl and tetrahydronaphthyl) and spiro rings are also included.

As used herein, the term "heterocycle" means, unless otherwise stated, a stable 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12-membered monocyclic, bicyclic or tricyclic ring (recognizing that rings with

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certain numbers of members cannot be bicyclic or tricyclic, e.g., a 3-membered ring can only be a monocyclic ring), which is saturated, unsaturated, or aromatic, and consists of carbon atoms and one or more ring heteroatoms, e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen, and sulfur, and including
5 any bicyclic or tricyclic group in which any of the above-defined heterocyclic rings is fused to a second ring (e.g., a benzene ring). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., $N \rightarrow O$ and $S(O)_p$, where $p = 1$ or 2). When a nitrogen atom is included in the ring it is either N or NH, depending on whether or not it is attached to a double bond in the ring (i.e., a hydrogen is present if needed to maintain the tri-valency of the nitrogen atom). The nitrogen
10 atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O
15 atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Preferred bridges include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two
20 nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Spiro and fused rings are also included.

As used herein, the term "aromatic heterocycle" or "heteroaryl" is intended to mean a stable 5, 6, 7, 8, 9, 10, 11, or 12-membered monocyclic or bicyclic aromatic ring (recognizing
25 that rings with certain numbers of members cannot be a bicyclic aromatic, e.g., a 5-membered ring can only be a monocyclic aromatic ring), which consists of carbon atoms and one or more heteroatoms, e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen, and sulfur. In the case of bicyclic heterocyclic aromatic rings, only one of the two rings needs to be aromatic (e.g., 2,3-dihydroindole), though
30 both may be (e.g., quinoline). The second ring can also be fused or bridged as defined above for heterocycles. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The nitrogen and sulfur heteroatoms may optionally be

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oxidized (i.e., $N \rightarrow O$ and $S(O)_p$, where $p = 1$ or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1*H*-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthroliny, phenaziny, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazoliny, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidinyl, pyrrolidinyl, pyrroliny, 2*H*-pyrrolyl, pyrrolyl, quinazoliny, quinoliny, 4*H*-quinoliziny, quinoxaliny, quinuclidiny, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example,

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from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic.

10 The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, USA, p. 1445 (1990).

 Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

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"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

As used herein, "treating" or "treatment" means the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

As used herein, "mammal" refers to human and non-human patients.

As used herein, the term "therapeutically effective amount" refers to a compound, or a combination of compounds, of the present invention present in or on a recipient in an amount sufficient to elicit biological activity, for example, anti-microbial activity, anti-fungal activity, anti-viral activity, anti-parasitic activity, and/or anti-proliferative activity. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* vol. 22, pp. 27-55 (1984), occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased anti-proliferative and/or anti-infective effect, or some other beneficial effect of the combination compared with the individual components.

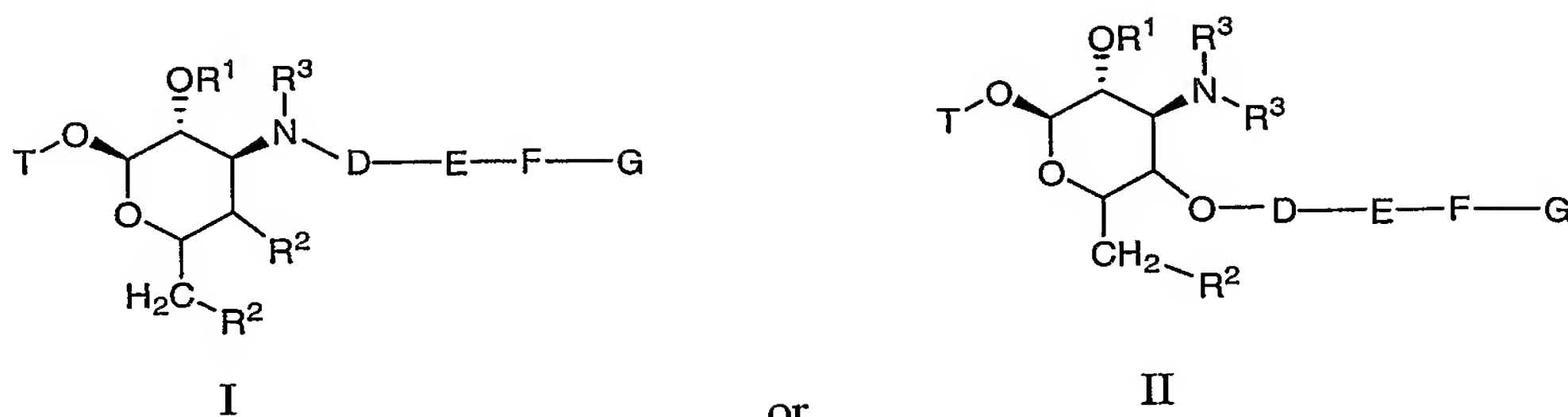
All percentages and ratios used herein, unless otherwise indicated, are by weight.

Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that compositions of the present invention also consist essentially of, or consist of, the recited components, and that the processes of the present invention also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions are immaterial so long as the invention remains operable. Moreover, two or more steps or actions may be conducted simultaneously.

2. Compounds of the Invention

In one aspect, the invention provides a compound having the formula:

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or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof, wherein

T is a 14-, 15-, or 16-membered macrolide connected via a macrocyclic ring carbon atom;

R¹ and R³ independently are selected from the group consisting of: (a) H, (b) a

- 5 C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group, (d) a C₂₋₆ alkynyl group, (e) -C(O)R⁵,
 (f) -C(O)OR⁵, (g) -C(O)-NR⁴R⁴R⁴R⁴, (h) -C(S)R⁵, (i) -C(S)OR⁵, (j) -C(O)SR⁵, or (k) -C(S)-
 NR⁴R⁴R⁴R⁴; R² is hydrogen or -OR¹²;

D is selected from the group consisting of:

- 10 (a) a single bond, (b) a C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group; (d) a C₂₋₆ alkynyl
 group; (e) -C(O)-X-, (f) -C(O)O-X-, (g) -C(O)NR⁴R⁴-X-,
 (h) -C(=NR⁴)-X-, (i) -C(=NR⁴)O-X-, (j) -C(=NR⁴)N-X-,
 (k) -SO₂-X-, (l) -C(NR⁴)NR⁴-X-, (m) -C(S)-X-,
 (n) -C(S)NR⁴-X-, (o) -C(NR⁴)S-X-, or (p) -C(O)S-X-, wherein
- 15 i) 0-2 carbon atoms in any of (b)-(d) of D immediately above
 optionally is replaced by a moiety selected from the group
 consisting of O, S(O)_p, and NR⁴,
- ii) each of the groups (b)-(d) immediately above optionally is
 substituted with one or more R⁵ groups,
- iii) alternatively when R⁵ is present as an optional substituent on (b)-
 20 (d), R³ and R⁵ can be taken together with the atoms to which they
 are attached to form a 3-7 membered ring, and
- iv) X is selected from the group consisting of (aa) a C₁₋₆ alkyl group,
 (bb) a C₂₋₆ alkenyl group, or (cc) a C₂₋₆ alkynyl group, wherein
 each of groups (aa)-(cc) optionally is substituted with one or more
 25 R⁵ groups;

F is selected from the group consisting of:

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(a) a single bond, (b) a C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group, (d) a C₂₋₆ alkynyl group, wherein

- i) 0-2 carbon atoms in any of (b)–(d) of F immediately above optionally is replaced by a moiety selected from the group consisting of O, S(O)_p, and NR⁴,
- ii) any of (b)–(d) of F immediately above optionally is substituted with one or more R⁵ groups, and
- iii) any of (b)–(d) of F immediately above optionally is substituted with C₁₋₆ alkyl-R⁵ groups;

E is selected from the group consisting of:

(a) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

(b) a 3-10 membered saturated, unsaturated, or aromatic carbocycle,

(c) a –W–[3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur],

(d) a –W–[3-10 membered saturated, unsaturated, or aromatic carbocycle],

(e) –C(O)–, (f) –C(O)O–, (g) –C(O)NR⁴–, (h) –C(=NR⁴)–,

(i) –C(=NR⁴)O–, (j) –C(=NR⁴)NR⁴–, (k) –OC(O)–, (l) –OC(O)O–,

(m) –OC(O)NR⁴–, (n) –NR⁴C(O)–, (o) –NR⁴C(O)O–,

(p) –NR⁴C(O)NR⁴–, (q) –NR⁴C(=NR⁴)NR⁴–, (r) –S(O)_p–,

(s) –NR⁴S(O)₂–, (t) –S(O)₂NR⁴–, (u) –C(N–OR⁴)–, (v) –CH₂–,

(w) –C(N–NR⁴R⁴)–, (x) –C(S)NR⁴–, (y) –NR⁴C(S)–, (z) –C(S)O–, or

(aa) –OC(S)–, wherein

- i) any of (a)–(d) immediately above optionally is substituted with one or more R⁵ groups; and

- ii) W is selected from the group consisting of:

(aa) –OCO–, (bb) –OC(O)O–, (cc) –OC(O)NR⁴–,

(dd) –NR⁴C(O)O–, (ee) –OCNOR⁴–,

(ff) –NR⁴–C(O)O–, (gg) –C(S)(NR⁴)–, (hh) –NR⁴–,

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(ii) $-\text{OC}(\text{S})\text{O}-$, (jj) $-\text{OC}(\text{S})\text{NR}^4-$, (kk) $-\text{NR}^4\text{C}(\text{S})\text{O}-$, (ll) $-\text{OC}(\text{S})\text{NOR}^4-$, (mm) $-\text{C}(\text{S})\text{O}-$, (nn) $-\text{OC}(\text{S})-$, (oo) $-\text{C}(\text{O})-$, (pp) $-\text{C}(\text{O})\text{O}-$, (qq) $-\text{C}(\text{O})\text{NR}^4-$, (rr) $-\text{C}(=\text{NR}^4)-$, (ss) $-\text{C}(=\text{NR}^4)\text{O}-$, (tt) $-\text{C}(=\text{NR}^4)\text{NR}^4-$, (uu) $-\text{OC}(\text{O})-$, (vv) $-\text{OC}(\text{O})\text{O}-$, (ww) $-\text{OC}(\text{O})\text{NR}^4-$, (xx) $-\text{NR}^4\text{C}(\text{O})-$, (yy) $-\text{NR}^4\text{C}(\text{O})\text{O}-$, (zz) $-\text{NR}^4\text{C}(\text{O})\text{NR}^4-$, (aaa) $-\text{NR}^4\text{C}(=\text{NR}^4)\text{NR}^4-$, (bbb) $-\text{S}(\text{O})_p-$, (ccc) $-\text{NR}^4\text{S}(\text{O})_2-$, (ddd) $-\text{S}(\text{O})_2\text{NR}^4-$, (eee) $-\text{C}(\text{N}-\text{OR}^4)-$, (fff) $-\text{C}(\text{N}-\text{NR}^4\text{R}^4)-$, (ggg) $-\text{C}(\text{S})\text{NR}^4-$, or (hhh) $-\text{NR}^4\text{C}(\text{S})-$;

10 G is selected from the group consisting of: (a) B' and (b) B'-Z-B'', wherein

i) each B' and B'' is independently selected from the group consisting of (aa) an aryl group, (bb) a heteroaryl group, (cc) a biaryl group, (dd) a fused bicyclic or tricyclic saturated, unsaturated or aromatic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (ee) a 3-10 membered saturated or unsaturated heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (ff) a 3-10 membered saturated, or unsaturated carbocycle, wherein each (aa)-(ff) optionally is substituted with one or more R¹¹ groups; and

ii) Z is selected from the group consisting of (aa) a single bond, (bb) a C₁₋₂ alkyl group, (cc) a C₂ alkenyl group, (dd) a C₂ alkynyl group, (ee) $-\text{C}(\text{O})-$, (ff) $-\text{C}(\text{O})\text{O}-$, (gg) $-\text{C}(\text{O})\text{NR}^4-$, (hh) $-\text{C}(=\text{NR}^4)-$, (ii) $-\text{C}(=\text{NR}^4)\text{O}-$, (jj) $-\text{C}(=\text{NR}^4)\text{NR}^4-$, (kk) $-\text{S}(\text{O})_p-$, (ll) $-\text{OC}(\text{O})-$, (mm) $-\text{C}(\text{S})-$, (nn) $-\text{C}(\text{S})\text{NR}^4-$, (oo) $-\text{C}(\text{NR}^4)\text{S}-$, (pp) $-\text{C}(\text{O})\text{S}-$, (qq) $-\text{O}-$, (rr) $-\text{NR}^4-$, (ss) $-\text{NR}^4\text{C}(\text{O})-$, (tt) $-\text{OC}(\text{NR}^4)-$, (uu) $-\text{NC}(\text{NR}^4)-$, (vv) $-\text{C}(\text{S})\text{O}-$, (ww) $-\text{SC}(\text{O})-$, or (xx) $-\text{OC}(\text{S})$;

R⁴, at each occurrence, independently is selected from the group consisting of:

30 (a) H, (b) a C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group, (d) a C₂₋₆ alkynyl group, (e) a C₆₋₁₀ saturated, unsaturated, or aromatic carbocycle, (f) a 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more

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heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,
 (g) $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl, (h) $-\text{C}(\text{O})-\text{C}_{2-6}$ alkenyl, (i) $-\text{C}(\text{O})-\text{C}_{2-6}$ alkynyl, (j) $-\text{C}(\text{O})-\text{C}_{6-10}$ saturated, unsaturated, or aromatic carbocycle, (k) $-\text{C}(\text{O})-3-12$ membered saturated, unsaturated, or aromatic heterocycle containing one or more

5 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,
 (l) $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl, (m) $-\text{C}(\text{O})\text{O}-\text{C}_{2-6}$ alkenyl, (n) $-\text{C}(\text{O})\text{O}-\text{C}_{2-6}$ alkynyl,
 (o) $-\text{C}(\text{O})\text{O}-\text{C}_{6-10}$ saturated, unsaturated, or aromatic carbocycle, (p) $-\text{C}(\text{O})\text{O}-3-12$ membered saturated, unsaturated, or aromatic heterocycle containing one or more
 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,
 10 and q) $-\text{C}(\text{O})\text{NR}^6\text{R}^6$,

wherein any of (b)–(p) optionally is substituted with one or more R^5 groups,

alternatively, NR^4R^4 forms a 3-7 membered saturated, unsaturated or aromatic ring including the nitrogen atom to which the R^4 groups are bonded, wherein said ring is optionally
 15 substituted at a position other than the nitrogen atom to which the R^4 groups are bonded, with one or more moieties selected from the group consisting of O, $\text{S}(\text{O})_p$, N, and NR^8 ;

R^5 is selected from the group consisting of:

(a) R^7 , (b) a C_{1-8} alkyl group, (c) a C_{2-8} alkenyl group, (d) a C_{2-8} alkynyl group, (e) a C_{3-12} saturated, unsaturated, or aromatic carbocycle, and (f) a 3-12 membered
 20 saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, or two R^5 groups, when present on the same carbon atom can be taken together with the carbon atom to which they are attached to form a spiro 3-6 membered carbocyclic ring or heterocyclic ring containing one or more heteroatoms selected
 25 form the group consisting of nitrogen, oxygen, and sulfur;

wherein any of (b)–(f) immediately above optionally is substituted with one or more R^7 groups;

R^6 , at each occurrence, independently is selected from the group consisting of:

(a) H, (b) a C_{1-6} alkyl group, (c) a C_{2-6} alkenyl group, (d) a C_{2-6} alkynyl group, (e) a C_{3-10} saturated, unsaturated, or aromatic carbocycle, and (f) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more
 30 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

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wherein any of (b)–(f) optionally is substituted with one or more moieties selected from the group consisting of:

- (aa) a carbonyl group, (bb) a formyl group, (cc) F, (dd) Cl, (ee) Br, (ff) I, (gg) CN, (hh) NO₂, (ii) –OR⁸,
 5 (jj) –S(O)_pR⁸, (kk) –C(O)R⁸, (ll) –C(O)OR⁸,
 (mm) –OC(O)R⁸, (nn) –C(O)NR⁸R⁸,
 (oo) –OC(O)NR⁸R⁸, (pp) –C(=NR⁸)R⁸,
 (qq) –C(R⁸)(R⁸)OR⁸, (rr) –C(R⁸)₂OC(O)R⁸,
 (ss) –C(R⁸)(OR⁸)(CH₂)_rNR⁸R⁸, (tt) –NR⁸R⁸,
 10 (uu) –NR⁸OR⁸, (vv) –NR⁸C(O)R⁸,
 (ww) –NR⁸C(O)OR⁸, (xx) –NR⁸C(O)NR⁸R⁸,
 (yy) –NR⁸S(O)_rR⁸, (zz) –C(OR⁸)(OR⁸)R⁸,
 (ab) –C(R⁸)₂NR⁸R⁸, (ac) =NR⁸,
 (ad) –C(S)NR⁸R⁸, (ae) –NR⁸C(S)R⁸,
 15 (af) –OC(S)NR⁸R⁸, (ag) –NR⁸C(S)OR⁸,
 (ah) –NR⁸C(S)NR⁸R⁸, (ai) –SC(O)R⁸,
 (aj) a C₁₋₈ alkyl group, (ak) a C₂₋₈ alkenyl group, (al) a C₂₋₈ alkynyl group, (am) a C₁₋₈ alkoxy group, (an) a C₁₋₈ alkylthio group, (ao) a C₁₋₈ acyl group, (ap) –CF₃,
 20 (aq) –SCF₃, (ar) a C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, and (as) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

alternatively, NR⁶R⁶ forms a 3-10 membered saturated, unsaturated or aromatic ring
 25 including the nitrogen atom to which the R⁶ groups are attached wherein said ring is optionally substituted at a position other than the nitrogen atom to which the R⁶ groups are bonded, with one or more moieties selected from the group consisting of O, S(O)_p, N, and NR⁸;

alternatively, CR⁶R⁶ forms a carbonyl group;

R⁷, at each occurrence, is selected from the group consisting of:

- 30 (a) H, (b) =O, (c) F, (d) Cl, (e) Br, (f) I, (g) –CF₃,
 (h) –CN, (i) –N₃, (j) –NO₂, (k) –NR⁶(CR⁶R⁶)_tR⁹, (l) –OR⁹, (m) –S(O)_pC(R⁶R⁶)_tR⁹,
 (n) –C(O)(CR⁶R⁶)_tR⁹, (o) –OC(O)(CR⁶R⁶)_tR⁹, (p) –SC(O)(CR⁶R⁶)_tR⁹, (q) –

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$C(O)O(CR^6R^6)_tR^9$, (r) $-NR^6C(O)(CR^6R^6)_tR^9$, (s) $-C(O)NR^6(CR^6R^6)_tR^9$, (t) $-$
 $C(=NR^6)(CR^6R^6)_tR^9$, (u) $-C(=NNR^6R^6)(CR^6R^6)_tR^9$, (v) $-$
 $C(=NNR^6C(O)R^6)(CR^6R^6)_tR^9$, (w) $-C(=NOR^9)(CR^6R^6)_tR^9$, (x) $-$
 $NR^6C(O)O(CR^6R^6)_tR^9$, (y) $-OC(O)NR^6(CR^6R^6)_tR^9$, (z) $-$
 $NR^6C(O)NR^6(CR^6R^6)_tR^9$, (aa) $-NR^6S(O)_p(CR^6R^6)_tR^9$, (bb) $-$
 $S(O)_pNR^6(CR^6R^6)_tR^9$, (cc) $-NR^6S(O)_pNR^6(CR^6R^6)_tR^9$, (dd) $-NR^6R^6$, (ee) $-$
 $NR^6(CR^6R^6)$, (ff) $-OH$, (gg) $-NR^6R^6$, (hh) $-OCH_3$, (ii) $-S(O)_pR^6$, (jj) $-NC(O)R^6$,
(kk) a C_{1-6} alkyl group, (ll) a C_{2-6} alkenyl group, (mm) a C_{2-6} alkynyl group, (nn) $-$
 C_{3-10} saturated, unsaturated, or aromatic carbocycle, and (oo) 3-10 membered
saturated, unsaturated, or aromatic heterocycle containing one or more
heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,
wherein any of (kk)–(oo) optionally is substituted with one or more R^9
groups;

alternatively, two R^7 groups may form $-O(CH_2)_uO-$;

R^8 is selected from the group consisting of:

(a) R^5 , (b) H, (c) a C_{1-6} alkyl group, (d) a C_{2-6} alkenyl group, (e) a C_{2-6} alkynyl
group, (f) a C_{3-10} saturated, unsaturated, or aromatic carbocycle, (g) a 3-10
membered saturated, unsaturated, or aromatic heterocycle containing one or more
heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,
(h) $-C(O)-C_{1-6}$ alkyl, (i) $-C(O)-C_{1-6}$ alkenyl, (j) $-C(O)-C_{1-6}$ alkynyl, (k) $-C(O)-$
 C_{3-10} saturated, unsaturated, or aromatic carbocycle, and (l) $-C(O)-3-10$
membered saturated, unsaturated, or aromatic heterocycle containing one or more
heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of (c)–(k) optionally is substituted with one or more moieties
selected from the group consisting of : (aa) H, (bb) F, (cc) Cl, (dd) Br, (ee)
I, (ff) CN, (gg) NO_2 , (hh) OH, (ii) NH_2 , (jj) $NH(C_{1-6}$ alkyl), (kk)
 $N(C_{1-6}$ alkyl) $_2$, (ll) a C_{1-6} alkoxy group, (mm) an aryl group, (nn) a
substituted aryl group, (oo) a heteroaryl group, (pp) a substituted
heteroaryl group, and qq) a C_{1-6} alkyl group optionally substituted with
one or more moieties selected from the group consisting of an aryl group,

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a substituted aryl group, a heteroaryl group, a substituted heteroaryl group,
F, Cl, Br, I, CN, NO₂, CF₃, SCF₃, and OH;

R⁹, at each occurrence, independently is selected from the group consisting of:

(a) R¹⁰, (b) a C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group, (d) a C₂₋₆ alkynyl group, e)
a C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, and f) a 3-10 membered
saturated, unsaturated, or aromatic heterocycle containing one or more
heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,
wherein any of (b)–(f) optionally is substituted with one or more R¹⁰
groups;

R¹⁰, at each occurrence, independently is selected from the group consisting of:

(a) H, (b) =O, (c) F, (d) Cl, (e) Br, (f) I, (g) –CF₃, (h) –CN, (i) –NO₂, (j) –NR⁶R⁶,
(k) –OR⁶, (l) –S(O)_pR⁶, (m) –C(O)R⁶, (n) –C(O)OR⁶, (o) –OC(O)R⁶, (p)
NR⁶C(O)R⁶, (q) –C(O)NR⁶R⁶, (r) –C(=NR⁶)R⁶, (s) –NR⁶C(O)NR⁶R⁶, (t) –
NR⁶S(O)_pR⁶, (u) –S(O)_pNR⁶R⁶, (v) –NR⁶S(O)_pNR⁶R⁶, (w) a C₁₋₆ alkyl group,
(x) a C₂₋₆ alkenyl group, (y) a C₂₋₆ alkynyl group, (z) a C₃₋₁₀ saturated,
unsaturated, or aromatic carbocycle, and (aa) a 3-10 membered saturated,
unsaturated, or aromatic heterocycle containing one or more heteroatoms selected
from the group consisting of nitrogen, oxygen, and sulfur,
wherein any of (w)–(aa) optionally is substituted with one or more
moieties selected from the group consisting of R⁶, F, Cl, Br, I, CN, NO₂, –
OR⁶, –NH₂, –NH(C₁₋₆ alkyl), –N(C₁₋₆ alkyl)₂, a C₁₋₆ alkoxy group, a
C₁₋₆ alkylthio group, and a C₁₋₆ acyl group;

R¹¹ each occurrence, independently is selected from the group consisting of:

(a) a carbonyl group, (b) a formyl group, (c) F, (d) Cl, (e) Br, (f) I, (g) CN, (h)
NO₂, (i) OR⁸, (j) –S(O)_pR⁸, (k) –C(O)R⁸, (l) –C(O)OR⁸,
(m) –OC(O)R⁸, (n) –C(O)NR⁸R⁸, (o) –OC(O)NR⁸R⁸,
(p) –C(=NR⁸)R⁸, (q) –C(R⁸)(R⁸)OR⁸, (r) –C(R⁸)₂OC(O)R⁸,
(s) –C(R⁸)(OR⁸)(CH₂)_rNR⁸R⁸, (t) –NR⁸R⁸, (u) –NR⁸OR⁸,
(v) –NR⁸C(O)R⁸, (w) –NR⁸C(O)OR⁸, (x) –NR⁸C(O)NR⁸R⁸, (y) –NR⁸S(O)_rR⁸, (z)
–C(OR⁸)(OR⁸)R⁸, (aa) –C(R⁸)₂NR⁸R⁸, (bb) =NR⁸, (cc) –C(S)NR⁸R⁸, (dd) –
NR⁸C(S)R⁸, (ee) –OC(S)NR⁸R⁸, (ff) –NR⁸C(S)OR⁸, (gg) –NR⁸C(S)NR⁸R⁸, (hh) –

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SC(O)R⁸, (ii) a C₁₋₈ alkyl group, (jj) a C₂₋₈ alkenyl group, (kk) a C₂₋₈ alkynyl group, (ll) a C₁₋₈ alkoxy group, (mm) a C₁₋₈ alkylthio group, (nn) a C₁₋₈ acyl group, (oo) a C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, and (pp) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, wherein (ii)-(kk) optionally are substituted with one or more R⁵ groups;

R¹² is selected from the group consisting of:

(a) H, (b) a C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group, (d) a C₂₋₆ alkynyl group, (e) -C(O)R⁵, (f) -C(O)OR⁵, (g) -C(O)-NR⁴R⁴R⁴, (h) -C(S)R⁵, (i) -C(S)OR⁵, (j) -C(O)SR⁵, (k) -C(S)-NR⁴R⁴R⁴, (l) a C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, or (m) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, (n) a -(C₁₋₆ alkyl) -C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, or (o) a -(C₁₋₆ alkyl)-3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, wherein (a)-(d) and (l)-(o) optionally are substituted with one or more R⁵ groups;

p at each occurrence is 0, 1, or 2;

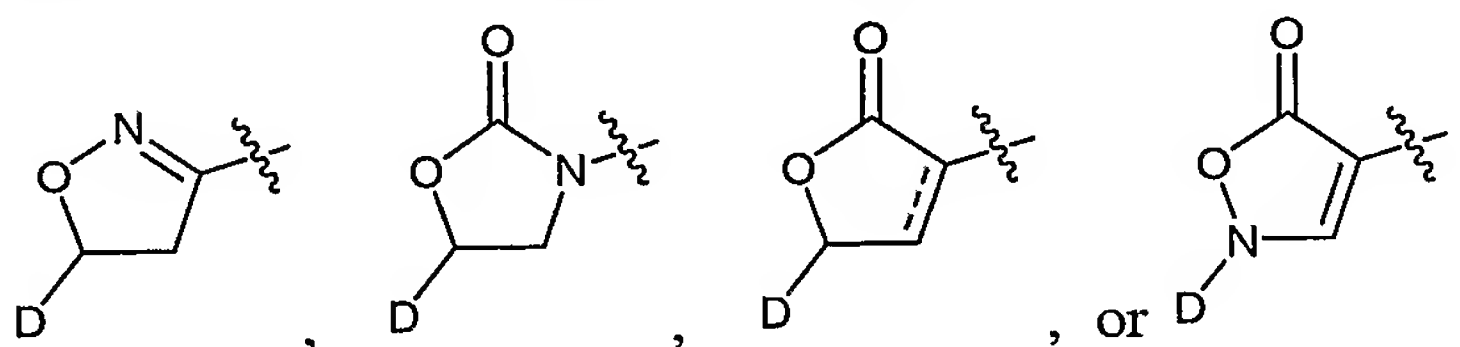
r at each occurrence is 0, 1, or 2;

t at each occurrence is 0, 1, or 2;

u at each occurrence is 1, 2, 3, or 4;

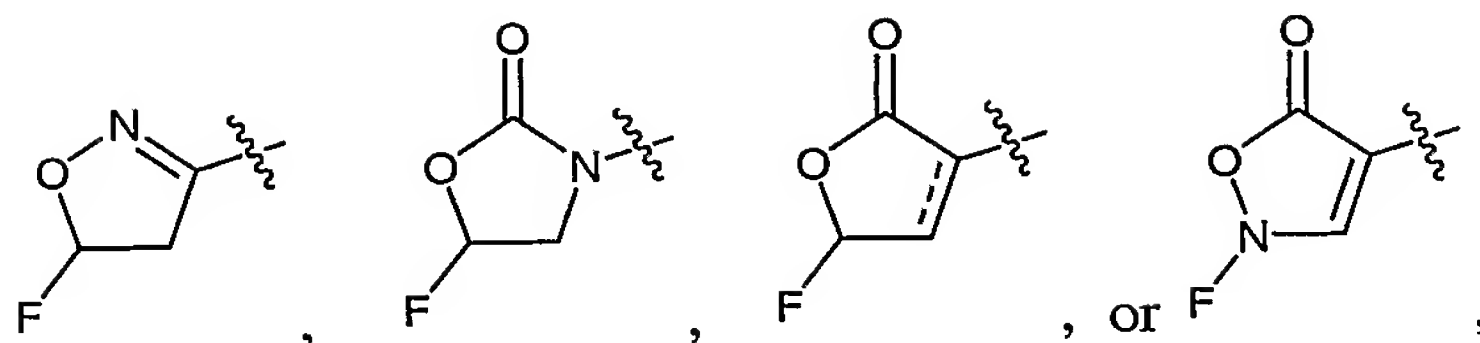
provided that

i) when T is a 14 or 15 membered macrolide D-E is not

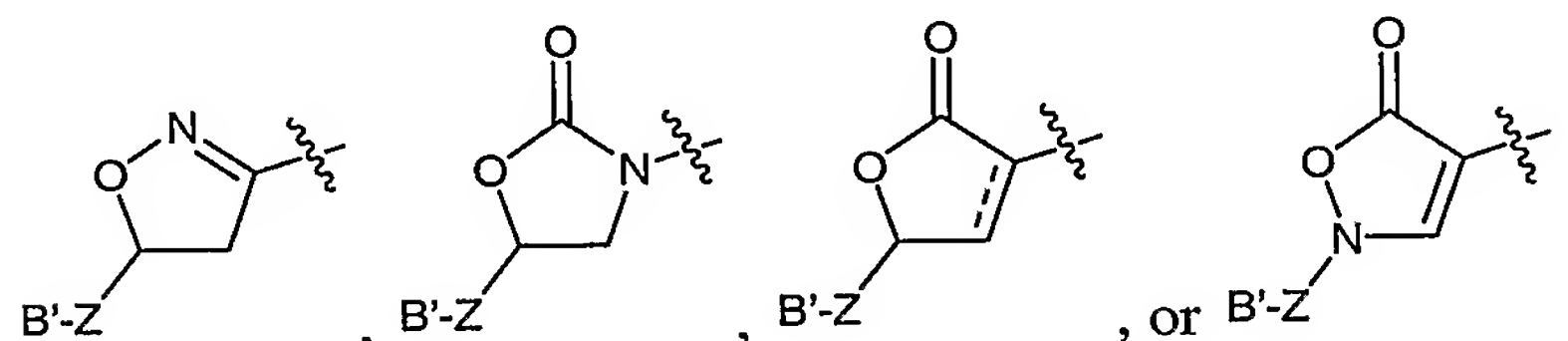


ii) when T is a 14 or 15 membered macrolide F-B' is not

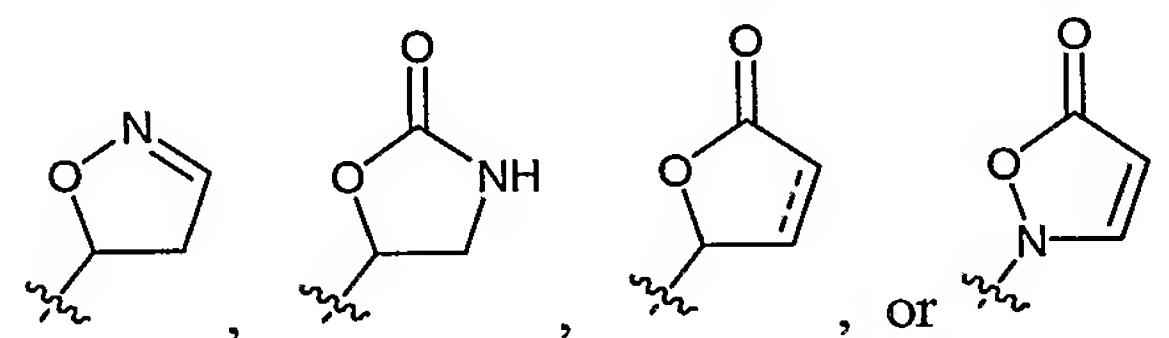
- 20 -



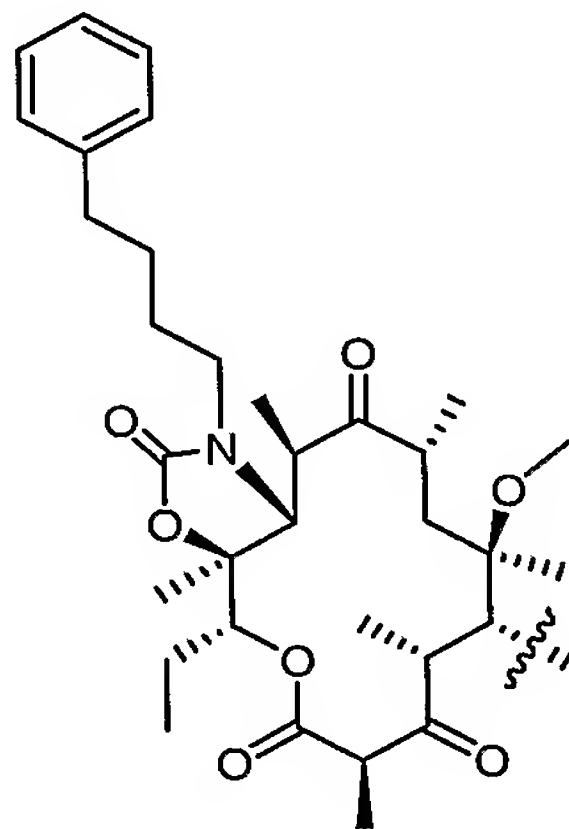
iii) when T is a 14 or 15 membered macrolide B'-Z-B'' is not



iv) when T is a 14 or 15 membered macrolide R¹¹ is not



v) when the compound has formula I and T is

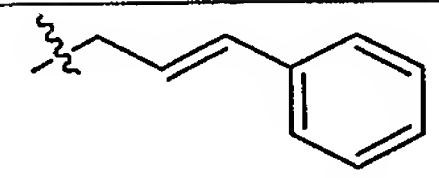
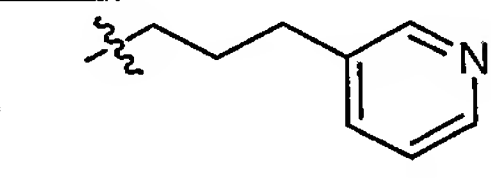
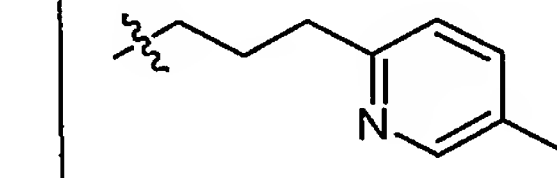
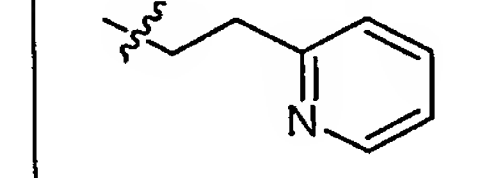
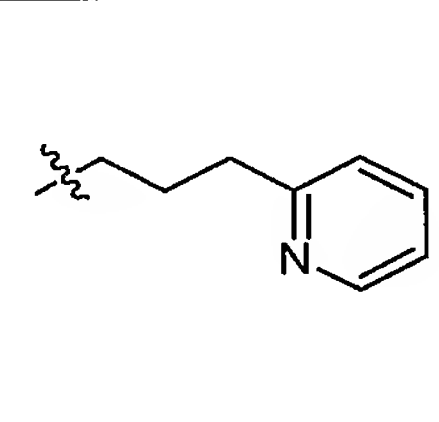
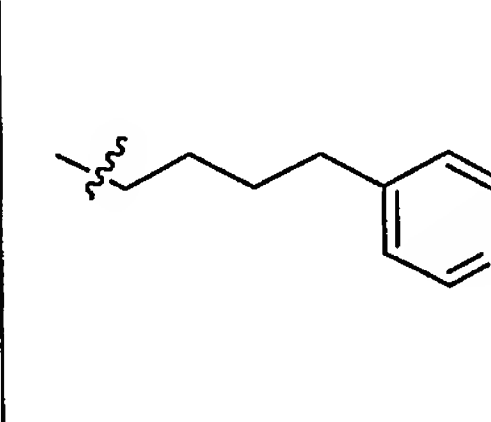
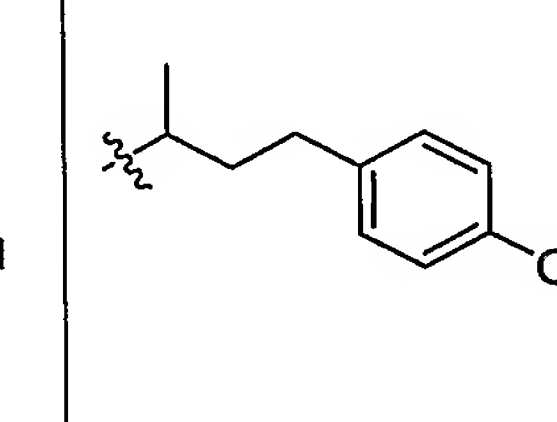
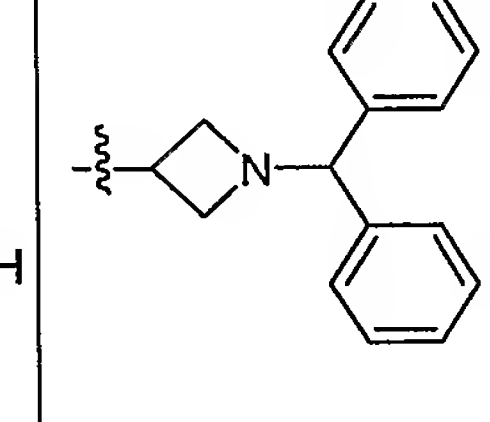
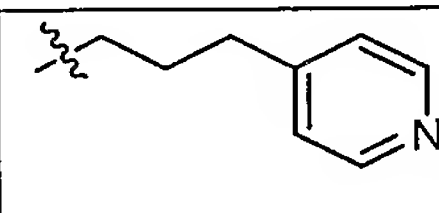
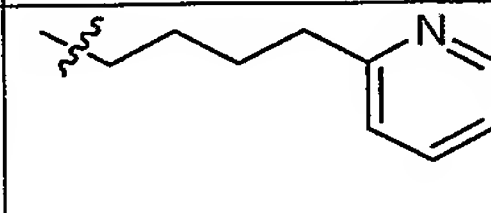
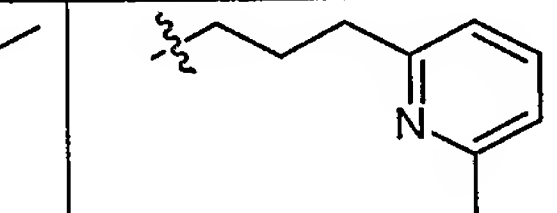


D is not a single bond or a -CH₂-,

vi) when the compound has formula I and T is a 14 or 15 membered macrolide -D-E-F- is not a -CH₂-,

vii) when the compound has formula I and T is a 14 or 15 membered macrolide -D-E-F-G- is not a chemical moiety selected from the chemical moieties listed in Table A

Table A

, and

20

viii) when the compound has formula II and T is a 16 membered macrolide

i. -D-E- is not a glycoside attached via its anomeric carbon,

ii. -D-E-F-G is not a C₁₋₄ (alkyl), C₂₋₄(alkenyl), or C₂₋₄(alkynyl)

chain bonded to a 5-10 membered monocyclic or bicyclic

carbocycle or heterocycle or bonded to a 5 or 6 membered

carbocycle or heterocycle bonded to a 5 or 6 membered carbocycle

or heterocycle, further, any of said carbocycles or heterocycles

being optionally substituted with one or more groups selected

from the group consisting of (aa) -OH, (bb) -F, (cc) -Cl, (dd) -I,

and (ee) -NO₂, and

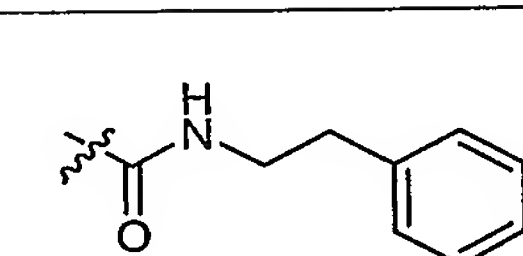
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iii. -D-E-F-G- is not a chemical moiety selected from the chemical

moieties listed in Table B.

30

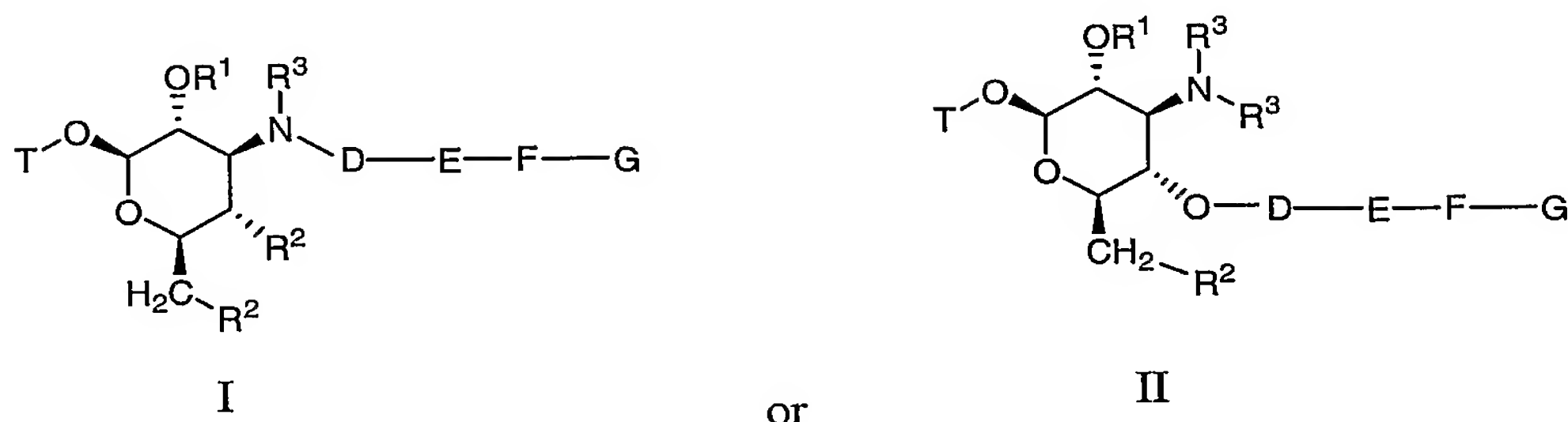
Table B

	<p>-(t-butoxycarboxy)-3-(3-quinolyl)</p>
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- 22 -

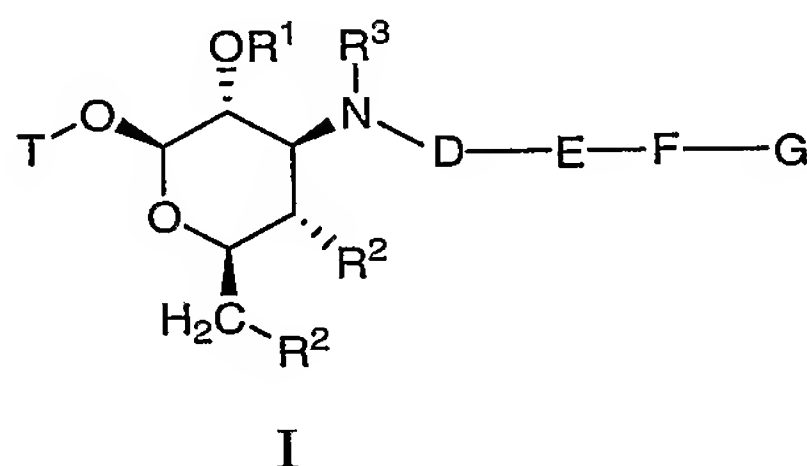
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In certain embodiments, the invention provides a compound having the formula:



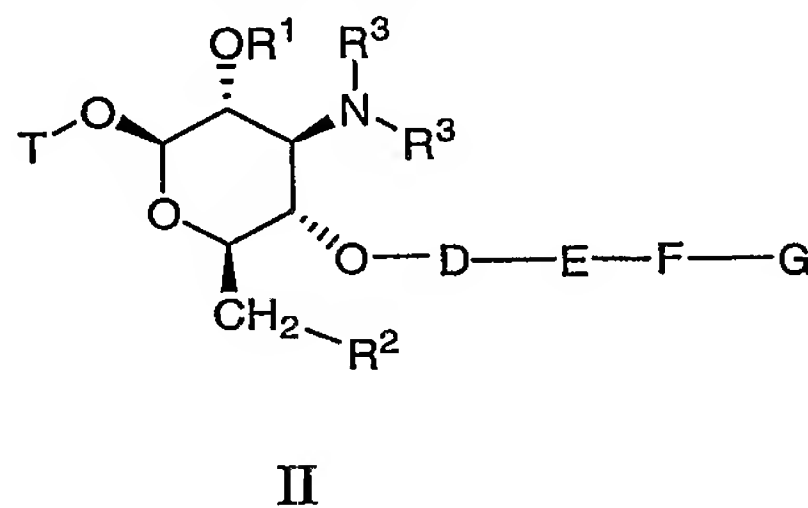
25 or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof, wherein T, D, E, F, G, R¹, R², and R³ are as defined hereinabove.

Other embodiments of the foregoing compounds include those compounds having the formula:



30 or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof, wherein T, D, E, F, G, R¹, R², and R³ are as defined hereinabove.

Other embodiments of the foregoing compounds include those having the formula:



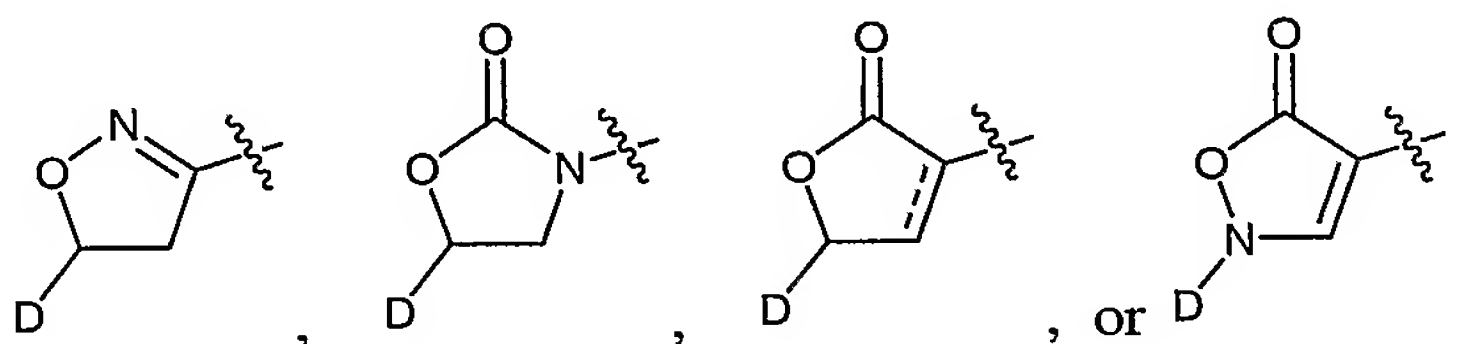
35 or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof, wherein T, D, E, F, G, R¹, R², and R³ are as defined hereinabove.

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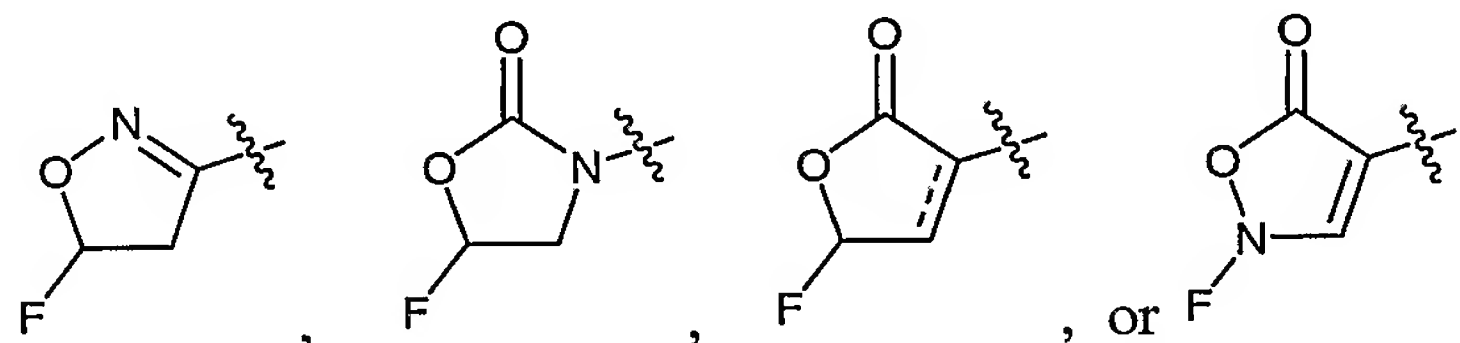
20 Other embodiments of the foregoing compounds include those where T is a 14- or 15-membered macrolide (i.e., not a 16 membered macrolide) connected via a macrocyclic ring carbon atom. In other embodiments, T is a 16 membered macrolide (i.e., not a 14 or 15 membered macrolide) connected via a macrocyclic ring carbon atom.

In certain other embodiments when T is a 14-, 15-, or 16-membered macrolide

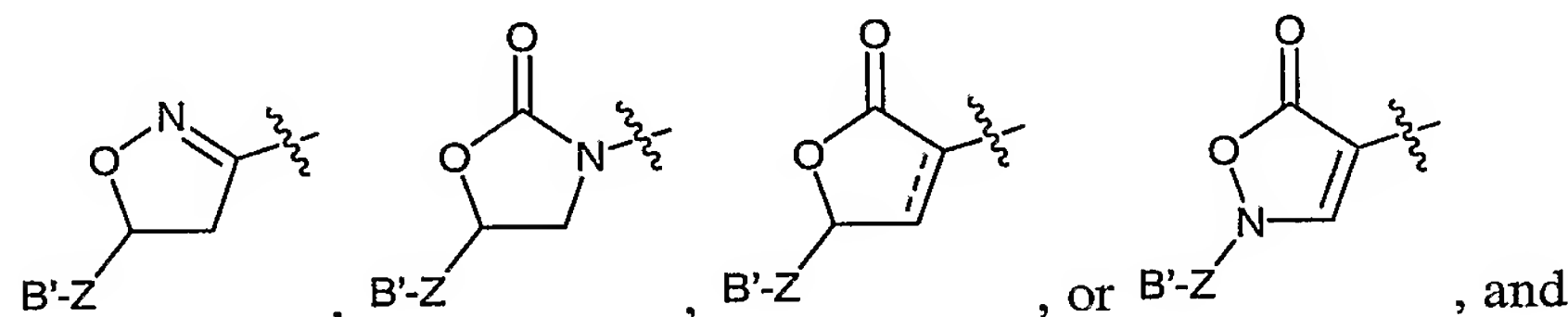
25 i) D-E is not



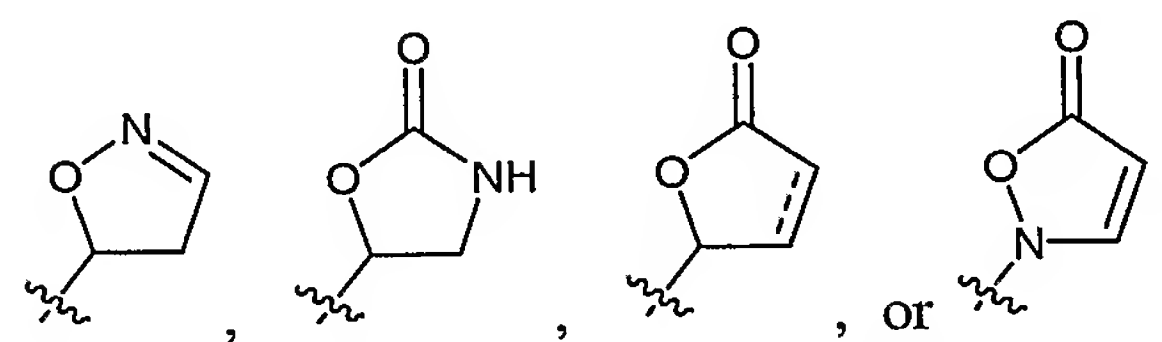
ii) F-B' is not



iii) B'-Z-B'' is not



iv) R¹¹ is not



Other embodiments of the foregoing compounds include those where G is B'.

35 Other embodiments of the foregoing compounds include those where B' is selected from the group consisting of: (a) an aryl group, (b) a heteroaryl group, (c) a biaryl group, and (d) a fused bicyclic or tricyclic unsaturated or aromatic ring system optionally containing one or more carbonyl groups and one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, wherein each (a)-(d) optionally is substituted with one or more R¹¹ groups.

Other embodiments of the foregoing compounds include those where E is

- 24 -

- 20 (a) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,
- (b) a 3-10 membered saturated, unsaturated, or aromatic carbocycle,
- 25 (c) a $-W-$ [3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur],
- (d) a $-W-$ [3-10 membered saturated, unsaturated, or aromatic carbocycle],
- (e) $-C(O)-$, (f) $-C(O)O-$, (g) $-C(O)NR^4-$, (h) $-C(=NR^4)-$,
- (i) $-C(=NR^4)O-$, (j) $-C(=NR^4)NR^4-$, (k) $-OC(O)-$, (l) $-OC(O)O-$,
- 30 (m) $-OC(O)NR^4-$, (n) $-NR^4C(O)-$, (o) $-NR^4C(O)O-$,
- (p) $-NR^4C(O)NR^4-$, (q) $-NR^4C(=NR^4)NR^4-$, (r) $-S(O)_p-$,
- (s) $-NR^4S(O)_2-$, (t) $-S(O)_2NR^4-$, (u) $-C(N-OR^4)-$, (v) $-C(N-NR^4R^4)-$,
- (w) $-C(S)NR^4-$, (x) $-NR^4C(S)-$, (y) $-C(S)O-$, or (z) $-OC(S)-$, wherein
- i) any of (a)-(d) immediately above optionally is substituted with one
- 35 or more R^5 groups; and
- ii) W is selected from the group consisting of:
- (aa) $-OCO-$, (bb) $-OC(O)O-$, (cc) $-OC(O)NR^4-$, (dd) $-NR^4C(O)O-$, (ee) $-OCNOR^4-$, (ff) $-NR^4-C(O)O-$, (gg) $-C(S)(NR^4)-$, (hh) $-NR^4-$, (ii) $-OC(S)O-$, (jj) $-OC(S)NR^4-$, (kk) $-NR^4C(S)O-$, (ll) $-OC(S)NOR^4-$, (mm) $-C(S)O-$, (nn) $-OC(S)-$,
- 40 (oo) $-C(O)-$, (pp) $-C(O)O-$, (qq) $-C(O)NR^4-$, (rr) $-C(=NR^4)-$, (ss) $-C(=NR^4)O-$, (tt) $-C(=NR^4)NR^4-$, (uu) $-OC(O)-$, (vv) $-OC(O)O-$, (ww) $-OC(O)NR^4-$, (xx) $-NR^4C(O)-$, (yy) $-NR^4C(O)O-$, (zz) $-NR^4C(O)NR^4-$, (aaa) $-NR^4C(=NR^4)NR^4-$,
- 45 (bbb) $-S(O)_p-$, (ccc) $-NR^4S(O)_2-$, (ddd) $-S(O)_2NR^4-$, (eee) $-C(N-OR^4)-$, (fff) $-C(N-NR^4R^4)-$, (ggg) $-C(S)NR^4-$, or (hhh) $-NR^4C(S)-$.

Other embodiments of the foregoing compounds include those where

D is selected from the group consisting of (a) a C_{1-6} alkyl group, (b) a C_{2-6} alkenyl group,

50 and (c) a C_{2-6} alkynyl group, wherein

- 25 -

- 20 i) 0-2 carbon atoms in any of (a)–(c) of D immediately above
optionally is replaced by a moiety selected from the group
consisting of O, S(O)_p, and NR⁴,
ii) any of (a)–(c) of D immediately above optionally is substituted with
one or more R⁵ groups; and

25 F is selected from the group consisting of (a) a single bond, (b) a C₁₋₆ alkyl group, (c) a
C₂₋₆ alkenyl group, and (d) a C₂₋₆ alkynyl group, wherein

- i) 0-2 carbon atoms in any of (b)–(d) of F immediately above
optionally is replaced by a moiety selected from the group
consisting of O, S(O)_p, and NR⁴;
30 ii) any of (b)–(d) of F immediately above optionally is substituted with
one or more R⁵ groups; and
iii) any of (b)–(d) of F immediately above optionally is substituted with
C₁₋₆ alkyl-R⁵.

Other embodiments of the foregoing compounds include those where E is selected from
35 the group consisting of:

- (a) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing
one or more heteroatoms selected from the group consisting of nitrogen, oxygen,
and sulfur,
(b) a 3-10 membered saturated, unsaturated, or aromatic carbocycle,
40 (c) a –W–[3-10 membered saturated, unsaturated, or aromatic heterocycle
containing one or more heteroatoms selected from the group consisting of
nitrogen, oxygen, and sulfur],
(d) a –W–[3-10 membered saturated, unsaturated, or aromatic carbocycle],
(e) –C(O)–, (f) –C(O)O–, (g) –C(O)NR⁴–, (h) –C(=NR⁴)–, (i) –C(=NR⁴)O–, (j) –
45 C(=NR⁴)NR⁴–, (k) –OC(O)–, (l) –OC(O)O–,
(m) –OC(O)NR⁴–, (n) –NR⁴C(O)–, (o) –NR⁴C(O)O–, (p) –NR⁴C(O)NR⁴–, (q) –
NR⁴C(=NR⁴)NR⁴–, (r) –S(O)_p–, (s) –NR⁴S(O)₂–, (t) –S(O)₂NR⁴–, (u) –C(N–
OR⁴)–, (v) –CH₂–, (w) –C(N–NR⁴R⁴)–, (x) –C(S)NR⁴, (Y) –NR⁴C(S)–, (Z) –
C(S)O–, or (aa) –OC(S)–, wherein
50 i) any of (a)–(d) immediately above optionally is substituted with one
or more R⁵ groups; and

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- 20 ii) W is selected from the group consisting of:
- (aa) $-\text{OCO}-$, (bb) $-\text{OC}(\text{O})\text{O}-$, (cc) $-\text{OC}(\text{O})\text{NR}^4-$,
 (dd) $-\text{NR}^4\text{C}(\text{O})\text{O}-$, (ee) $-\text{OCNOR}^4-$,
 (ff) $-\text{NR}^4-\text{C}(\text{O})\text{O}-$, (gg) $-\text{C}(\text{S})(\text{NR}^4)-$, (hh) $-\text{NR}^4$,
 (ii) $-\text{OC}(\text{S})\text{O}-$, (jj) $-\text{OC}(\text{S})\text{NR}^4-$, (kk) $-\text{NR}^4\text{C}(\text{S})\text{O}-$, (ll) $-\text{OC}(\text{S})\text{NOR}^4-$, (mm) $-\text{C}(\text{S})\text{O}-$, (nn) $-\text{OC}(\text{S})$, (oo) $-\text{C}(\text{O})-$, (pp) $-\text{C}(\text{O})\text{O}-$, (qq) $-\text{C}(\text{O})\text{NR}^4-$, (rr) $-\text{C}(=\text{NR}^4)-$,
25 (ss) $-\text{C}(=\text{NR}^4)\text{O}-$, (tt) $-\text{C}(=\text{NR}^4)\text{NR}^4-$, (uu) $-\text{OC}(\text{O})-$, (vv) $-\text{OC}(\text{O})\text{O}-$, (ww) $-\text{OC}(\text{O})\text{NR}^4-$, (xx) $-\text{NR}^4\text{C}(\text{O})-$, (yy) $-\text{NR}^4\text{C}(\text{O})\text{O}-$, (zz) $-\text{NR}^4\text{C}(\text{O})\text{NR}^4-$, (aaa) $-\text{NR}^4\text{C}(=\text{NR}^4)\text{NR}^4-$,
30 (bbb) $-\text{S}(\text{O})_p-$, (ccc) $-\text{NR}^4\text{S}(\text{O})_2-$, (ddd) $-\text{S}(\text{O})_2\text{NR}^4-$, (eee) $-\text{C}(\text{N}-\text{OR}^4)-$, (fff) $-\text{C}(\text{N}-\text{NR}^4\text{R}^4)-$, (ggg) $-\text{C}(\text{S})\text{NR}^4-$, or (hhh) $-\text{NR}^4\text{C}(\text{S})-$.

Other embodiments of the foregoing compounds include those where E is selected from the group consisting of:

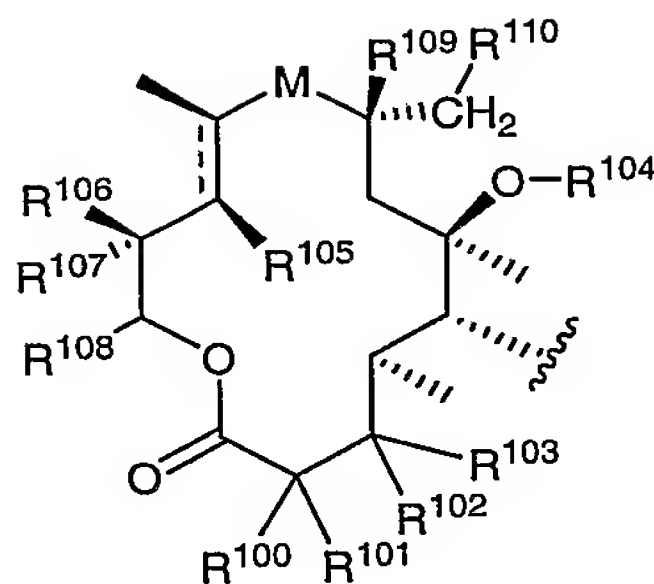
- 35 (a) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and
 (b) a 3-10 membered saturated, unsaturated, or aromatic carbocycle,
 wherein (a) and (b) immediately above optionally is substituted with one more R^5
40 groups.

Other embodiments of the foregoing compounds include those where E is selected from the group consisting of:

- 45 (a) $-\text{C}(\text{O})-$, (b) $-\text{C}(\text{O})\text{O}-$, (c) $-\text{C}(\text{O})\text{NR}^4-$, (d) $-\text{C}(=\text{NR}^4)-$,
 (e) $-\text{C}(=\text{NR}^4)\text{O}-$, (f) $-\text{C}(=\text{NR}^4)\text{NR}^4-$, (g) $-\text{OC}(\text{O})-$, (h) $-\text{OC}(\text{O})\text{O}-$, (i) $-\text{OC}(\text{O})\text{NR}^4-$, (j) $-\text{NR}^4\text{C}(\text{O})-$, (k) $-\text{NR}^4\text{C}(\text{O})\text{O}-$, (l) $-\text{NR}^4\text{C}(\text{O})\text{NR}^4-$, (m) $-\text{NR}^4\text{C}(=\text{NR}^4)\text{NR}^4-$, (n) $-\text{S}(\text{O})_p-$, (o) $-\text{NR}^4\text{S}(\text{O})_2-$, (p) $-\text{S}(\text{O})_2\text{NR}^4-$, (q) $-\text{C}(\text{N}-\text{OR}^4)-$, (r) $-\text{CH}_2-$, (s) $-\text{C}(\text{N}-\text{NR}^4\text{R}^4)-$, (t) $-\text{C}(\text{S})\text{NR}^4$, (u) $-\text{NR}^4\text{C}(\text{S})-$, (v) $-\text{C}(\text{S})\text{O}$,
 and (w) $-\text{OC}(\text{S})-$.

Other embodiments of the foregoing compounds include those where T is:

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or an N-oxide, pharmaceutically acceptable salt, ester or prodrug thereof,

wherein:

M is selected from the group consisting of:

- 25 (a) $-C((O)-$, (b) $-CH(-OR^{114})-$, (c) $-NR^{114}-CH_2-$, (d) $-CH_2-NR^{114}-$, (e) $-CH(NR^{114}R^{114})-$, (f) $-C(=NNR^{114}R^{114})-$, (g) $-NR^{114}-C(O)-$, (h) $-C(O)NR^{114}-$, (i) $-C(=NR^{114})-$, and (j) $-CR^{115}R^{115}-$, (k) $-C(=NOR^{127})-$;

R^{100} is selected from the group consisting of H and C_{1-6} alkyl;

R^{101} is selected from the group consisting of:

- 30 (a) H, (b) Cl, (c) F, (d) Br, (e) I, (f) $-NR^{114}R^{114}$, (g) $-NR^{114}C(O)R^{114}$, (h) $-OR^{114}$, (i) $-OC(O)R^{114}$, (j) $-OC(O)OR^{114}$, (k) $-OC(O)NR^{114}R^{114}$, (l) $-O-C_{1-6}$ alkyl, (m) $-OC(O)-C_{1-6}$ alkyl, (n) $-OC(O)O-C_{1-6}$ alkyl, (o) $-OC(O)NR^{114}-C_{1-6}$ alkyl, (p) C_{1-6} alkyl, (q) C_{1-6} alkenyl, (r) C_{1-6} alkynyl,

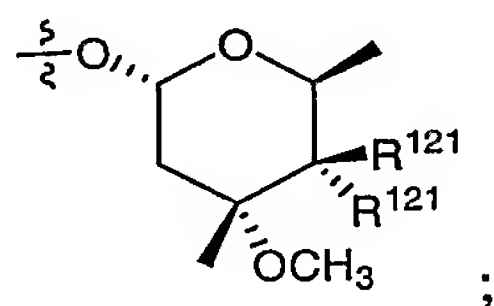
wherein any of (l) – (r) optionally is substituted with one or more

- 35 R^{115} groups;

R^{102} is H;

R^{103} is selected from the group consisting of:

- 40 (a) H, (b) $-OR^{114}$, (c) $-O-C_{1-6}$ alkyl- R^{115} , (d) $-OC((O)R^{114})$, (e) $-OC(O)-C_{1-6}$ alkyl- R^{115} , (f) $-OC(O)OR^{114}$, (g) $-OC(O)O-C_{1-6}$ alkyl- R^{115} , (h) $-OC(O)NR^{114}R^{114}$, (i) $-OC(O)NR^{114}-C_{1-6}$ alkyl- R^{115} , and (j)



alternatively, R^{102} and R^{103} taken together form a carbonyl group;

- 28 -

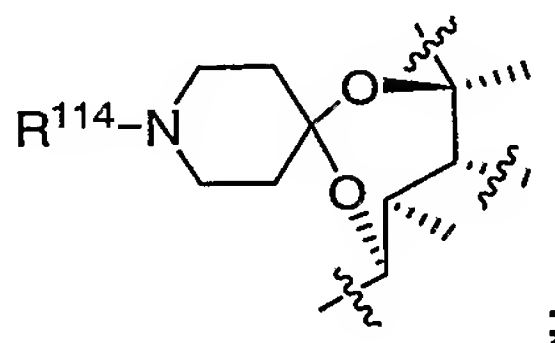
20 alternatively, R^{101} and R^{103} taken together are a single bond between the respective carbons to which these two groups are attached thereby creating a double bond between the carbons to which R^{100} and R^{102} are attached;

alternatively, R^{101} and R^{103} taken together are an epoxide moiety.

R^{104} is selected from the group consisting of:

25 (a) H, (b) R^{114} , (c) $-C(O)R^{114}$ (d) $-C(O)OR^{114}$ (e) $-C(O)NR^{114}R^{114}$, (f) $-C_{1-6}$ alkyl- $K-R^{114}$, (g) $-C_{2-6}$ alkenyl- $K-R^{114}$, and (h) $-C_{2-6}$ alkynyl- $K-R^{114}$;

alternatively R^{103} and R^{104} , taken together with the atoms to which they are bonded, form:



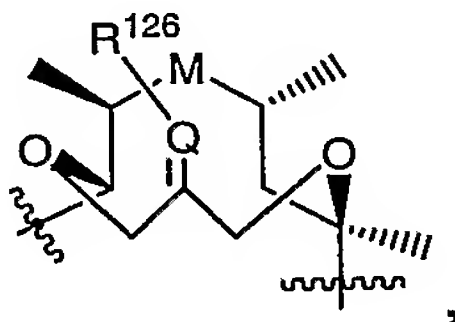
K is selected from the group consisting of:

30 (a) $-C(O)-$, (b) $-C(O)O-$, (c) $-C(O)NR^{114}-$, (d) $-C(=NR^{114})-$, (e) $-C(=NR^{114})O-$, (f) $-C(=NR^{114})NR^{114}-$, (g) $-OC(O)-$, (h) $-OC(O)O-$, (i) $-OC(O)NR^{114}-$, (j) $-NR^{114}C(O)-$, (k) $-NR^{114}C(O)O-$, (l) $-NR^{114}C(O)NR^{114}-$, (m) $-NR^{114}C(=NR^{114})NR^{114}-$, and (o) $-S(O)_p-$;

R^{105} is selected from the group consisting of:

35 (a) R^{114} , (b) $-OR^{114}$, (c) $-NR^{114}R^{114}$, (d) $-O-C_{1-6}$ alkyl- R^{115} , (e) $-C(O)-R^{114}$, (f) $-C(O)-C_{1-6}$ alkyl- R^{115} , (g) $-OC(O)-R^{114}$, (h) $-OC(O)-C_{1-6}$ alkyl- R^{115} , (i) $-OC(O)O-R^{114}$, (j) $-OC(O)O-C_{1-6}$ alkyl- R^{115} , (k) $-OC(O)NR^{114}R^{114}$, (l) $-OC(O)NR^{114}-C_{1-6}$ alkyl- R^{115} , (m) $-C(O)-C_{2-6}$ alkenyl- R^{115} , and (n) $-C(O)-C_{2-6}$ alkynyl- R^{115} ;

40 alternatively, R^{104} and R^{105} , taken together with the atoms to which they are bonded, form:

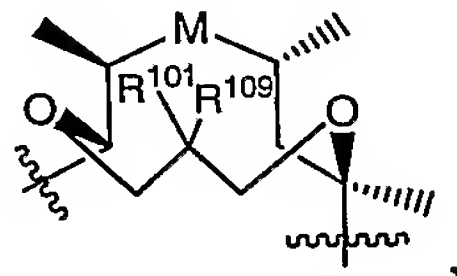


wherein

Q is CH or N, and R^{126} is $-OR^{114}$, $-NR^{114}$ or R^{114} ;

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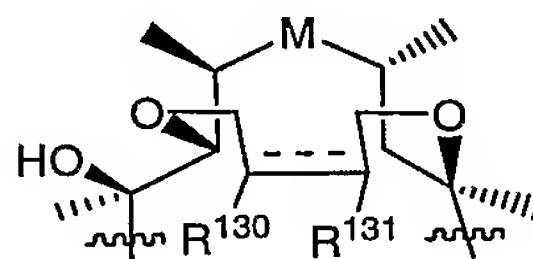
20 alternatively, R^{104} and R^{105} , taken together with the atoms to which they are bonded, form:



wherein

- 25 i) R^{101} is as defined above;
 ii) alternately, R^{101} and R^{109} may be taken together form a carbonyl group;
 iii) alternately, R^{101} and R^{109} may be taken together to form the group $-O(CR^{116}R^{116})_uO-$;

30 alternatively, R^{104} and R^{105} , taken together with the atoms to which they are bonded, form:



- 35 i) R^{130} is $-OH$, $=C(O)$, or R^{114} ,
 ii) R^{131} is $-OH$, $=C(O)$, or R^{114} ,
 iii) alternately, R^{130} and R^{131} together with the carbons to which they are attached form a 3-7 membered saturated, unsaturated or aromatic carbocyclic or heterocyclic ring which can optionally be substituted with one or more R^{114} groups;

R^{106} is selected from the group consisting of:

- 40 (a) $-OR^{114}$, (b) $-C_{1-6}$ alkoxy- R^{115} , (c) $-C(O)R^{114}$, (d) $-OC(O)R^{114}$, (e) $-OC(O)OR^{114}$, (f) $-OC(O)NR^{114}R^{114}$, and (g) $-NR^{114}R^{114}$,

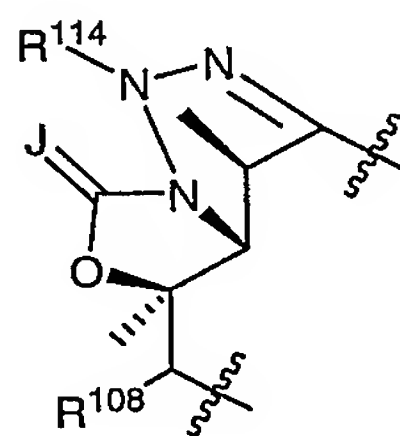
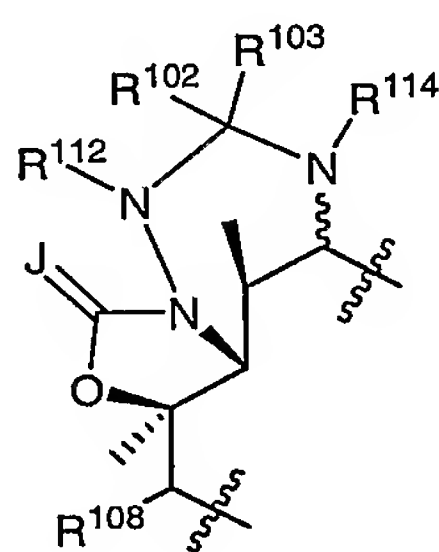
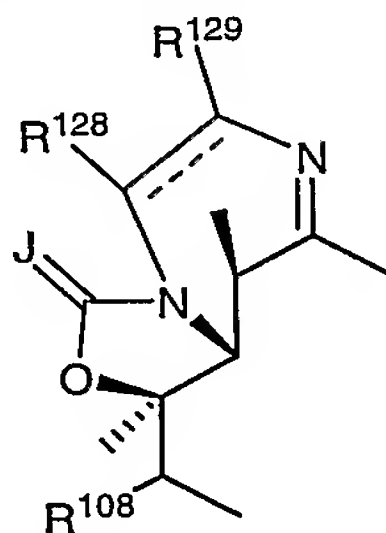
alternatively, R^{105} and R^{106} taken together with the atoms to which they are attached form a 5-membered ring by attachment to each other through a chemical moiety selected from the group consisting of:

- 45 (a) $-OC(R^{115})_2O-$, (b) $-OC(O)O-$, (c) $-OC(O)NR^{114}-$, (d) $-NR^{114}C(O)O-$,
 (e) $-OC(O)NOR^{114}-$, (f) $-NOR^{114}-C(O)O-$, (g) $-OC(O)NNR^{114}R^{114}-$,

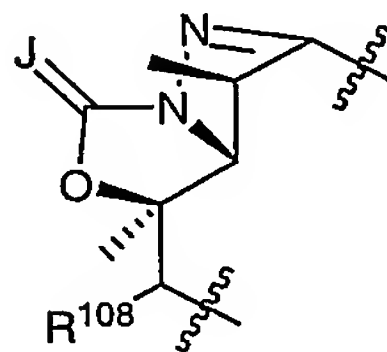
- 30 -

- 20 (h) $-\text{NNR}^{114}\text{R}^{114}-\text{C}(\text{O})\text{O}-$, (i) $-\text{OC}(\text{O})\text{C}(\text{R}^{115})_2-$, (j) $-\text{C}(\text{R}^{115})_2\text{C}(\text{O})\text{O}-$, (k) $-\text{OC}(\text{S})\text{O}-$, (l) $-\text{OC}((\text{S})\text{NR}^{114})-$, (m) $-\text{NR}^{114}\text{C}(\text{S})\text{O}-$, (n) $-\text{OC}(\text{S})\text{NOR}^{114}-$, (o) $-\text{NOR}^{114}-\text{C}(\text{S})\text{O}-$, (p) $-\text{OC}(\text{S})\text{NNR}^{114}\text{R}^{114}-$, (q) $-\text{NNR}^{114}\text{R}^{114}-\text{C}(\text{S})\text{O}-$, (r) $-\text{OC}(\text{S})\text{C}(\text{R}^{115})_2-$, and (s) $-\text{C}(\text{R}^{115})_2\text{C}(\text{S})\text{O}-$;

alternatively, M, R^{105} , and R^{106} taken together with the atoms to which they are attached form:



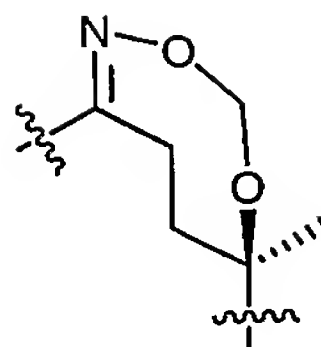
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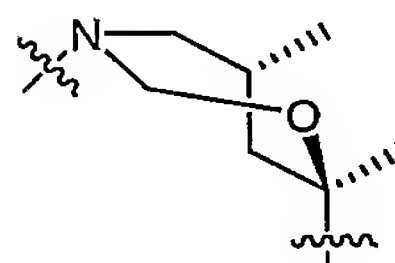
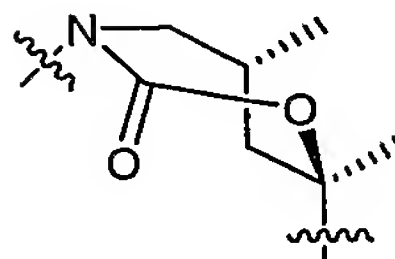
wherein J is selected from the group consisting of O, S and NR^{114} ;

alternatively, M and R^{104} taken together with the atoms to which they are attached form:

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25

R^{107} is selected from the group consisting of

- (a) H, (b) $-C_{1-4}$ alkyl, (c) $-C_{2-4}$ alkenyl, which can be further substituted with C_{1-12} alkyl or one or more halogens, (d) $-C_{2-4}$ alkynyl, which can be further substituted with C_{1-12} alkyl or one or more halogens, (e) aryl or heteroaryl, which can be further substituted with C_{1-12} alkyl or one or more halogens, (f) $-C(O)H$, (g) $-COOH$, (h) $-CN$, (i) $-COOR^{114}$, (j) $-C(O)NR^{114}R^{114}$, (k) $-C(O)R^{114}$, and (l) $-C(O)SR^{114}$, wherein (b) is further substituted with one or more substituents selected from the group consisting of (aa) $-OR^{114}$, (bb) halogen, (cc) $-SR^{114}$, (dd) C_{1-12} alkyl, which can be further substituted with halogen, hydroxyl, C_{1-6} alkoxy, or amino, (ee) $-OR^{114}$, (ff) $-SR^{114}$, (gg) $-NR^{114}R^{114}$, (hh) $-CN$, (ii) $-NO_2$, (jj) $-NC(O)R^{114}$, (kk) $-COOR^{114}$, (ll) $-N_3$, (mm) $=N-O-R^{114}$, (nn) $=NR^{114}$, (oo) $=N-NR^{114}R^{114}$, (pp) $=N-NH-C(O)R^{114}$, and (qq) $=N-NH-C(O)NR^{114}R^{114}$;

30

35

alternatively R^{106} and R^{107} are taken together with the atom to which they are attached to form an epoxide, a carbonyl, an olefin, or a substituted olefin, or a C_3-C_7 carbocyclic, carbonate, or carbamate, wherein the nitrogen of said carbamate can be further substituted with a C_1-C_6 alkyl;

40

R^{108} is selected from the group consisting of:

- (a) C_{1-6} alkyl, (b) C_{2-6} alkenyl, and (c) C_{2-6} alkynyl,

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20 wherein any of (a)–(c) optionally is substituted with one or more R^{114} groups;

R^{111} is selected from the group consisting of H and $-C(O)R^{114}$;

R^{112} is selected from the group consisting of H, OH, and OR^{114} ;

R^{113} is selected from the group consisting of:

25 (a) H, (b) R^{114} , (c) $-C_{1-6}$ alkyl- $K-R^{114}$, (d) $-C_{2-6}$ alkenyl- $K-R^{114}$, and
(e) $-C_{2-6}$ alkynyl- $K-R^{114}$,

wherein any of (c)–(e) optionally is substituted with one or more R^{115} groups;

R^{114} , at each occurrence, independently is selected from the group consisting of:

30 (a) H, (b) C_{1-6} alkyl, (c) C_{2-6} alkenyl, (d) C_{2-6} alkynyl, (e) C_{6-10} saturated,
unsaturated, or aromatic carbocycle, (f) 3-12 membered saturated, unsaturated, or
aromatic heterocycle containing one or more heteroatoms selected from the group
consisting of nitrogen, oxygen, and sulfur, (g) $-C(O)-C_{1-6}$ alkyl, (h) $-C(O)-$
35 C_{2-6} alkenyl, (i) $-C(O)-C_{2-6}$ alkynyl, (j) $-C(O)-C_{6-10}$ saturated, unsaturated, or
aromatic carbocycle, (k) $-C(O)-3-12$ membered saturated, unsaturated, or
aromatic heterocycle containing one or more heteroatoms selected from the group
consisting of nitrogen, oxygen, and sulfur, (l) $-C(O)O-C_{1-6}$ alkyl, (m) $-C(O)O-$
40 C_{2-6} alkenyl, (n) $-C(O)O-C_{2-6}$ alkynyl, (o) $-C(O)O-C_{6-10}$ saturated, unsaturated,
or aromatic carbocycle, (p) $-C(O)O-3-12$ membered saturated, unsaturated, or
aromatic heterocycle containing one or more heteroatoms selected from the group
consisting of nitrogen, oxygen, and sulfur, and (q) $-C(O)NR^{116}R^{116}$,

wherein any of (b)–(p) optionally is substituted with one or more R^{115} groups, wherein one or more non-terminal carbon moieties of any of (b)–
(d) optionally is replaced with oxygen, $S(O)_p$, or $-NR^{116}$,

45 alternatively, $NR^{114}R^{114}$ forms a 3-7 membered saturated, unsaturated or aromatic ring
including the nitrogen atom to which the R^{114} groups are bonded and optionally one or more
moieties selected from the group consisting of O, $S(O)_p$, N, and NR^{118} ;

R^{115} is selected from the group consisting of:

50 (a) R^{117} , (b) C_{1-8} alkyl, (c) C_{2-8} alkenyl, (d) C_{2-8} alkynyl, (e) C_{3-12} saturated,
unsaturated, or aromatic carbocycle, (f) 3-12 membered saturated, unsaturated, or

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20 aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of (b)–(f) optionally is substituted with one or more R^{117} groups;

R^{116} , at each occurrence, independently is selected from the group consisting of:

25 (a) H, (b) C_{1-6} alkyl, (c) C_{2-6} alkenyl, (d) C_{2-6} alkynyl, (e) C_{3-10} saturated, unsaturated, or aromatic carbocycle, and (f) 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

30 wherein one or more non-terminal carbon moieties of any of (b)–(d) optionally is replaced with oxygen, $S(O)_p$, or $-NR^{114}$, wherein any of (b)–(f) optionally is substituted with one or more moieties selected from the group consisting of:

35 (aa) carbonyl, (bb) formyl, (cc) F, (dd) Cl, (ee) Br, (ff) I, (gg) CN, (hh) N_3 , (ii) NO_2 , (jj) OR^{118} , (kk) $-S(O)_pR^{118}$, (ll) $-C(O)R^{118}$, (mm) $-C(O)OR^{118}$, (nn) $-OC(O)R^{118}$, (oo) $-C(O)NR^{118}R^{118}$, (pp) $-OC(O)NR^{118}R^{118}$, (qq) $-C(=NR^{118})R^{118}$, (rr) $-C(R^{118})(R^{118})OR^{118}$, (ss) $-C(R^{118})_2OC(O)R^{118}$, (tt) $-C(R^{118})(OR^{118})(CH_2)_rNR^{118}R^{118}$, (uu) $-NR^{118}R^{118}$, (vv) $-NR^{118}OR^{118}$, (ww) $-NR^{118}C(O)R^{118}$, (xx) $-NR^{118}C(O)OR^{118}$, (yy) $-NR^{118}C(O)NR^{118}R^{118}$, (zz) $-NR^{118}S(O)_rR^{118}$, (ab) $-C(OR^{118})(OR^{118})R^{118}$, (ac) $-C(R^{118})_2NR^{118}R^{118}$, (ad) $=NR^{118}$, (ae) $-C(S)NR^{118}R^{118}$, (af) $-NR^{118}C(S)R^{118}$, (ag) $-OC(S)NR^{118}R^{118}$, (ah) $-NR^{118}C(S)OR^{118}$, (ai) $-NR^{118}C(S)NR^{118}R^{118}$, (aj) $-SC(O)R^{118}$, (ak) C_{1-8} alkyl, (al) C_{2-8} alkenyl, (am) C_{2-8} alkynyl, (an) C_{1-8} alkoxy, (ao) C_{1-8} alkylthio, (ap) C_{1-8} acyl, (aq) saturated, unsaturated, or aromatic C_{3-10} carbocycle, and (ar) saturated, unsaturated, or aromatic 3-10 membered heterocycle containing one or more heteroatoms

45 selected from the group consisting of nitrogen, oxygen, and sulfur,

alternatively, $NR^{116}R^{116}$ forms a 3-10 membered saturated, unsaturated or aromatic ring
50 including the nitrogen atom to which the R^{116} groups are attached and optionally one or more moieties selected from the group consisting of O, $S(O)_p$, N, and NR^{118} ;

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20 alternatively, $\text{CR}^{116}\text{R}^{116}$ forms a carbonyl group;
 R^{117} , at each occurrence, is selected from the group consisting of:

(a) H, (b) =O, (c) F, (d) Cl, (e) Br, (f) I, (g) $(\text{CR}^{116}\text{R}^{116})_r\text{CF}_3$, (h) $(\text{CR}^{116}\text{R}^{116})_r\text{CN}$,
 (i) $(\text{CR}^{116}\text{R}^{116})_r\text{NO}_2$, (j) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (k) $(\text{CR}^{116}\text{R}^{116})_r\text{OR}^{119}$,
 (l) $(\text{CR}^{116}\text{R}^{116})_r\text{S}(\text{O})_p(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (m) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(\text{O})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$,
 25 (n) $(\text{CR}^{116}\text{R}^{116})_r\text{OC}(\text{O})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (o) $(\text{CR}^{116}\text{R}^{116})_r\text{SC}(\text{O})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$,
 (p) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(\text{O})\text{O}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (q) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}\text{C}(\text{O})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (r) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(\text{O})\text{NR}^{116}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (s)
 $(\text{CR}^{116}\text{R}^{116})_r\text{C}(=\text{NR}^{116})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$,
 (t) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(=\text{NNR}^{116}\text{R}^{116})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$,
 30 (u) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(=\text{NNR}^{116}\text{C}(\text{O})\text{R}^{116})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$,
 (v) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(=\text{NOR}^{119})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$,
 (w) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}\text{C}(\text{O})\text{O}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$,
 (x) $(\text{CR}^{116}\text{R}^{116})_r\text{OC}(\text{O})\text{NR}^{116}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$,
 (y) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}\text{C}(\text{O})\text{NR}^{116}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$,
 35 (z) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}\text{S}(\text{O})_p(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$,
 (aa) $(\text{CR}^{116}\text{R}^{116})_r\text{S}(\text{O})_p\text{NR}^{116}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$,
 (bb) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}\text{S}(\text{O})_p\text{NR}^{116}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (cc) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}\text{R}^{116}$,
 (dd) C_{1-6} alkyl, (ee) C_{2-6} alkenyl, (ff) C_{2-6} alkynyl, (gg) $(\text{CR}^{116}\text{R}^{116})_r\text{C}_{3-10}$
 saturated, unsaturated, or aromatic carbocycle, and (hh) $(\text{CR}^{116}\text{R}^{116})_r\text{C}_{3-10}$
 40 membered saturated, unsaturated, or aromatic heterocycle containing one or more
 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,
 wherein any of (dd)–(hh) optionally is substituted with one or more R^{119}
 groups;

alternatively, two R^{117} groups may form $-\text{O}(\text{CH}_2)_u\text{O}-$;

45 R^{118} is selected from the group consisting of:

(a) H, (b) C_{1-6} alkyl, (c) C_{2-6} alkenyl, (d) C_{2-6} alkynyl, (e) C_{3-10} saturated,
 unsaturated, or aromatic carbocycle, (f) 3-10 membered saturated, unsaturated, or
 aromatic heterocycle containing one or more heteroatoms selected from the group
 consisting of nitrogen, oxygen, and sulfur, (g) $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl, (h) $-\text{C}(\text{O})-$
 50 C_{1-6} alkenyl, (g) $-\text{C}(\text{O})-\text{C}_{1-6}$ alkynyl, (i) $-\text{C}(\text{O})-\text{C}_{3-10}$ saturated, unsaturated, or
 aromatic carbocycle, and (j) $-\text{C}(\text{O})-3-10$ membered saturated, unsaturated, or

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20 aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of (b)–(j) optionally is substituted with one or more moieties selected from the group consisting of : (aa) H, (bb) F, (cc) Cl, (dd) Br, (ee) I, (ff) CN, (gg) NO₂, (hh) OH, (ii) NH₂, (jj) NH(C₁₋₆ alkyl), (kk) N(C₁₋₆ alkyl)₂, (ll) C₁₋₆ alkoxy, (mm) aryl, (nn) substituted aryl, (oo) heteroaryl, (pp) substituted heteroaryl, and (qq) C₁₋₆ alkyl, optionally substituted with one or more moieties selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, F, Cl, Br, I, CN, NO₂, and OH;

30 R¹¹⁹, at each occurrence, independently is selected from the group consisting of: (a) R¹²⁰, (b) C₁₋₆ alkyl, (c) C₂₋₆ alkenyl, (d) C₂₋₆ alkynyl, (e) C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, and (f) 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

35 wherein any of (b)–(f) optionally is substituted with one or more R¹¹⁹ groups;

R¹²⁰, at each occurrence, independently is selected from the group consisting of:

(a) H, (b) =O, (c) F, (d) Cl, (e) Br, (f) I, (g) (CR¹¹⁶R¹¹⁶)_rCF₃, (h) (CR¹¹⁶R¹¹⁶)_rCN, (i) (CR¹¹⁶R¹¹⁶)_rNO₂, (j) (CR¹¹⁶R¹¹⁶)_rNR¹¹⁶R¹¹⁶, (k) (CR¹¹⁶R¹¹⁶)_rOR¹¹⁴, (l) (CR¹¹⁶R¹¹⁶)_rS(O)_pR¹¹⁶, (m) (CR¹¹⁶R¹¹⁶)_rC(O)R¹¹⁶, (n) (CR¹¹⁶R¹¹⁶)_rC(O)OR¹¹⁶, (o) (CR¹¹⁶R¹¹⁶)_rOC(O)R¹¹⁶, (p) (CR¹¹⁶R¹¹⁶)_rNR¹¹⁶C(O)R¹¹⁶, (q) (CR¹¹⁶R¹¹⁶)_rC(O)NR¹¹⁶R¹¹⁶, (r) (CR¹¹⁶R¹¹⁶)_rC(=NR¹¹⁶)R¹¹⁶, (s) (CR¹¹⁶R¹¹⁶)_rNR¹¹⁶C(O)NR¹¹⁶R¹¹⁶, (t) (CR¹¹⁶R¹¹⁶)_rNR¹¹⁶S(O)_pR¹¹⁶, (u) (CR¹¹⁶R¹¹⁶)_rS(O)_pNR¹¹⁶R¹¹⁶, (v) (CR¹¹⁶R¹¹⁶)_rNR¹¹⁶S(O)_pNR¹¹⁶R¹¹⁶, (w) C₁₋₆ alkyl, (x) C₂₋₆ alkenyl, (y) C₂₋₆ alkynyl, (z) (CR¹¹⁶R¹¹⁶)_r–C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, and (aa) (CR¹¹⁶R¹¹⁶)_r–3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, wherein any of (w)–(aa) optionally is substituted with one or more moieties selected from the group consisting of R¹¹⁶, F, Cl, Br, I, CN, NO₂,

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20 $-OR^{116}$, $-NH_2$, $-NH(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})_2$, C_{1-6} alkoxy,
 C_{1-6} alkylthio, and C_{1-6} acyl;

R^{121} , at each occurrence, independently is selected from the group consisting of:

(a) H, (b) $-OR^{118}$, (c) $-O-C_{1-6} \text{ alkyl}-OC(O)R^{118}$, (d) $-O-C_{1-6} \text{ alkyl}-OC(O)OR^{118}$,
 (e) $-O-C_{1-6} \text{ alkyl}-OC(O)NR^{118}R^{118}$, (f) $-O-C_{1-6} \text{ alkyl}-C(O)NR^{118}R^{118}$, (g) $-O-$
 25 $C_{1-6} \text{ alkyl}-NR^{118}C(O)R^{118}$, (h) $-O-C_{1-6} \text{ alkyl}-NR^{118}C(O)OR^{118}$, (i) $-O-C_{1-6} \text{ alkyl}-$
 $NR^{118}C(O)NR^{118}R^{118}$, (j) $-O-C_{1-6} \text{ alkyl}-NR^{118}C(=N(H)NR^{118}R^{118})$, (k) $-O-$
 $C_{1-6} \text{ alkyl}-S(O)_pR^{118}$, (l) $-O-C_{2-6} \text{ alkenyl}-OC(O)R^{118}$, (m) $-O-C_{2-6} \text{ alkenyl}-$
 $OC(O)OR^{118}$, (n) $-O-C_{2-6} \text{ alkenyl}-OC(O)NR^{118}R^{118}$, (o) $-O-C_{2-6} \text{ alkenyl}-$
 $C(O)NR^{118}R^{118}$, (p) $-O-C_{2-6} \text{ alkenyl}-NR^{118}C(O)R^{118}$, (q) $-O-C_{2-6} \text{ alkenyl}-$
 30 $NR^{118}C(O)OR^{118}$, (r) $-O-C_{2-6} \text{ alkenyl}-NR^{118}C(O)NR^{118}R^{118}$, (s) $-O-C_{2-6} \text{ alkenyl}-$
 $NR^{118}C(=N(H)NR^{118}R^{118})$, (t) $-O-C_{2-6} \text{ alkenyl}-S(O)_pR^{118}$,
 (u) $-O-C_{2-6} \text{ alkynyl}-OC(O)R^{118}$, (v) $-O-C_{2-6} \text{ alkynyl}-OC(O)OR^{118}$,
 (w) $-O-C_{2-6} \text{ alkynyl}-OC(O)NR^{118}R^{118}$, (x) $-O-C_{2-6} \text{ alkynyl}-C(O)NR^{118}R^{118}$, (y) $-$
 $O-C_{2-6} \text{ alkynyl}-NR^{118}C(O)R^{118}$, (z) $-O-C_{2-6} \text{ alkynyl}-NR^{118}C(O)OR^{118}$, (aa) $-O-$
 35 $C_{2-6} \text{ alkynyl}-NR^{118}C(O)NR^{118}R^{118}$,
 (bb) $-O-C_{2-6} \text{ alkynyl}-NR^{118}C(=N(H)NR^{118}R^{118})$, (cc) $-O-C_{2-6} \text{ alkynyl}-S(O)_pR^{118}$,
 and (dd) $-NR^{118}R^{118}$;

alternatively, two R^{121} groups taken together form $=O$, $=NOR^{118}$, or $=NNR^{118}R^{118}$;
 R^{122} is R^{115} ;

40 R^{123} is selected from the group consisting of:

(a) R^{116} , (b) F, (c) Cl, (d) Br, (e) I, (f) CN, (g) NO_2 , and (h) $-OR^{114}$;

alternatively, R^{122} and R^{123} taken together are $-O(CH_2)_uO-$;

R^{124} , at each occurrence, independently is selected from the group consisting of:

(a) H, (b) F, (c) Cl, (d) Br, (e) I, (f) CN, (g) $-OR^{114}$, (h) $-NO_2$, (i) $-NR^{114}R^{114}$, (j)
 45 C_{1-6} alkyl, (k) C_{1-6} acyl, and (l) C_{1-6} alkoxy;

R^{125} is selected from the group consisting of:

(a) C_{1-6} alkyl, (b) C_{2-6} alkenyl, (c) C_{2-6} alkynyl, (d) C_{1-6} acyl, (e) C_{1-6} alkoxy,
 (f) C_{1-6} alkylthio, (g) saturated, unsaturated, or aromatic C_{5-10} carbocycle,
 (h) saturated, unsaturated, or aromatic 5-10 membered heterocycle containing one
 50 or more heteroatoms selected from the group consisting of nitrogen, oxygen, and
 sulfur, (i) $-O-C_{1-6} \text{ alkyl-saturated, unsaturated, or aromatic 5-10 membered}$

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20 heterocycle containing one or more heteroatoms selected from the group
 consisting of nitrogen, oxygen, and sulfur, (j) $-\text{NR}^{114}-\text{C}_{1-6}$ alkyl-saturated,
 unsaturated, or aromatic 5-10 membered heterocycle containing one or more
 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,
 (k) saturated, unsaturated, or aromatic 10-membered bicyclic ring system
 25 optionally containing one or more heteroatoms selected from the group consisting
 of nitrogen, oxygen, and sulfur, (l) saturated, unsaturated, or aromatic 13-
 membered tricyclic ring system optionally containing one or more heteroatoms
 selected from the group consisting of nitrogen, oxygen, and sulfur, (m) $-\text{OR}^{114}$,
 (n) $-\text{NR}^{114}\text{R}^{114}$, (o) $-\text{S}(\text{O})_p\text{R}^{114}$, and (p) $-\text{R}^{124}$,

30 wherein any of (a)-(l) optionally is substituted with one or more R^{115}
 groups;

alternatively, R^{125} and one R^{124} group, taken together with the atoms to which they are
 bonded, form a 5-7 membered saturated or unsaturated carbocycle, optionally substituted with
 one or more R^{115} groups; or a 5-7 membered saturated or unsaturated heterocycle containing one
 35 or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally
 substituted with one or more R^{115} groups;

R^{126} at each occurrence, independently is selected from the group consisting of:

(a) hydrogen, (b) an electron-withdrawing group, (c) aryl, (d) substituted aryl,
 (e) heteroaryl, (f) substituted heteroaryl, and (g) C_{1-6} alkyl, optionally substituted
 40 with one or more R^{115} groups;

alternatively, any R^{126} and any R^{123} , taken together with the atoms to which they are
 bonded, form a 5-7 membered saturated or unsaturated carbocycle, optionally substituted with
 one or more R^{115} groups; or a 5-7 membered saturated or unsaturated heterocycle containing one
 or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally
 45 substituted with one or more R^{115} groups;

R^{109} is H or F;

R^{127} is R^{114} , a monosaccharide or disaccharide (including amino sugars and halo sugar(s),
 $-(\text{CH}_2)_n-(\text{O}-\text{CH}_2\text{CH}_2-)_m-\text{O}(\text{CH}_2)_p\text{CH}_3$ or $-(\text{CH}_2)_n-(\text{O}-\text{CH}_2\text{CH}_2-)_m-\text{OH}$

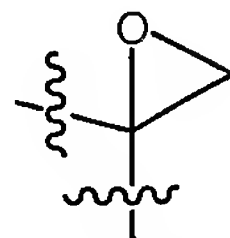
R^{128} is R^{114}

50 R^{129} is R^{114}

R^{110} is R^{114}

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20 Alternatively, R^{109} and R^{110} taken together with the carbons to which they are attached form:

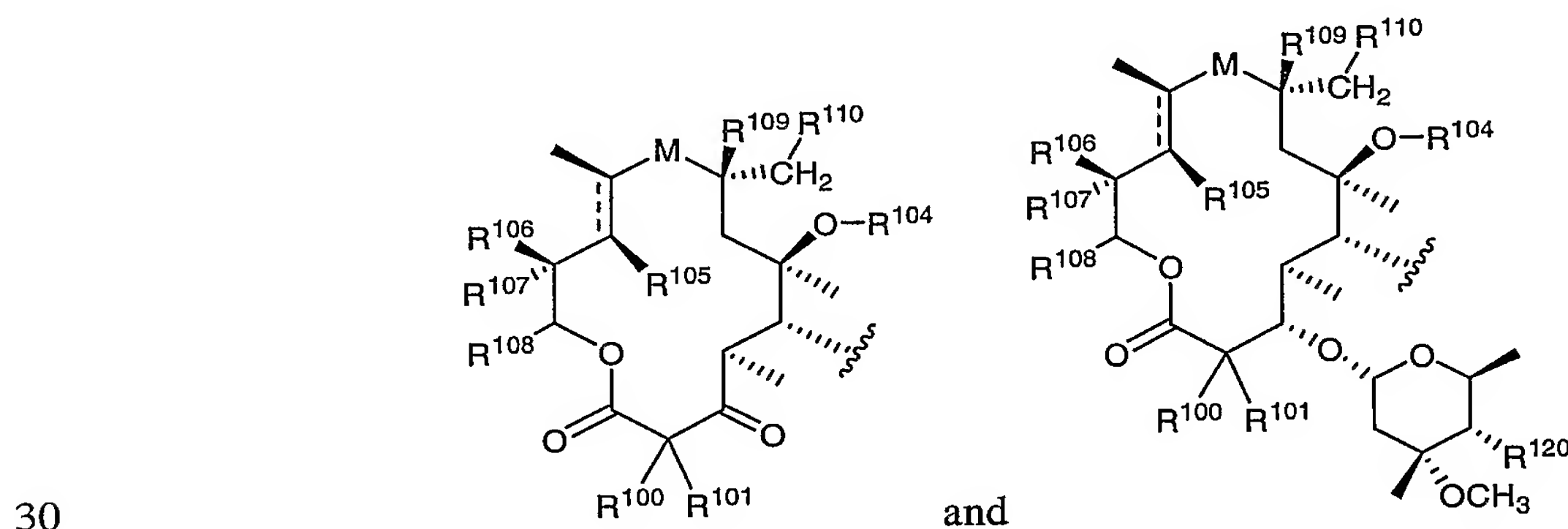


25 Alternately, R^{128} and R^{129} together with the carbons to which they are attached form a 3-6 membered saturated, unsaturated or aromatic carbocyclic or heterocyclic ring which may optionally be substituted with one or more R^{114} groups;

m, at each occurrence is 0, 1, 2, 3, 4, or 5;

n, at each occurrence is 1, 2, or 3.

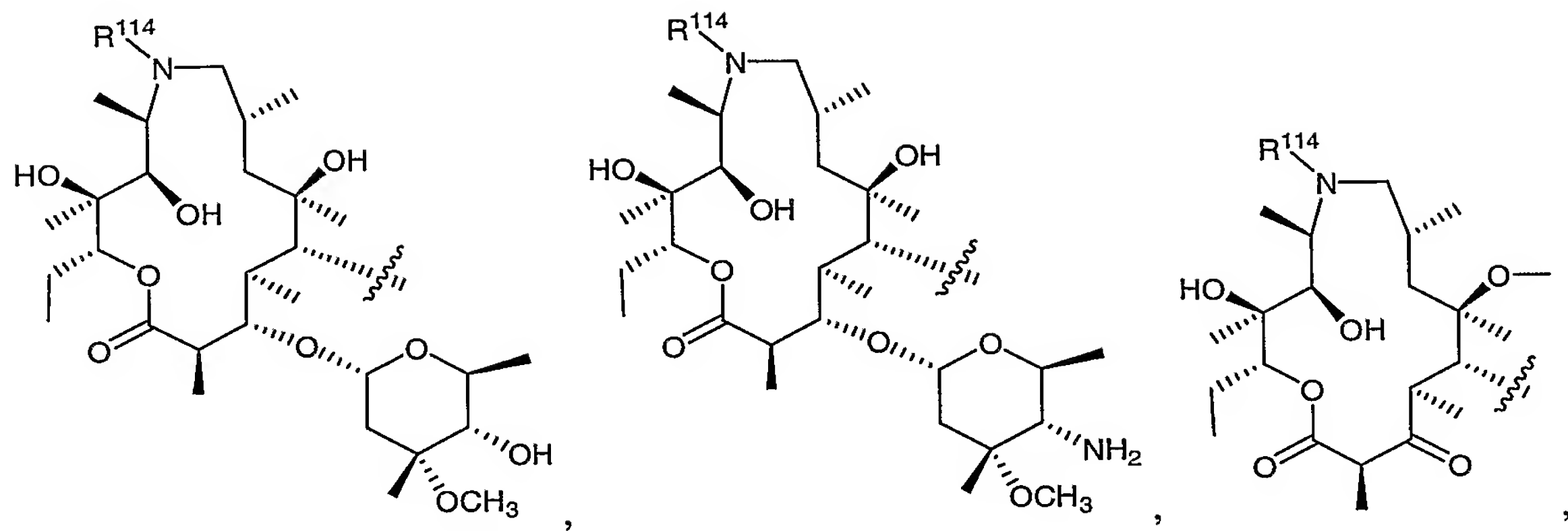
Other embodiments of the foregoing compounds include those where T is a macrolide selected from the group consisting of:



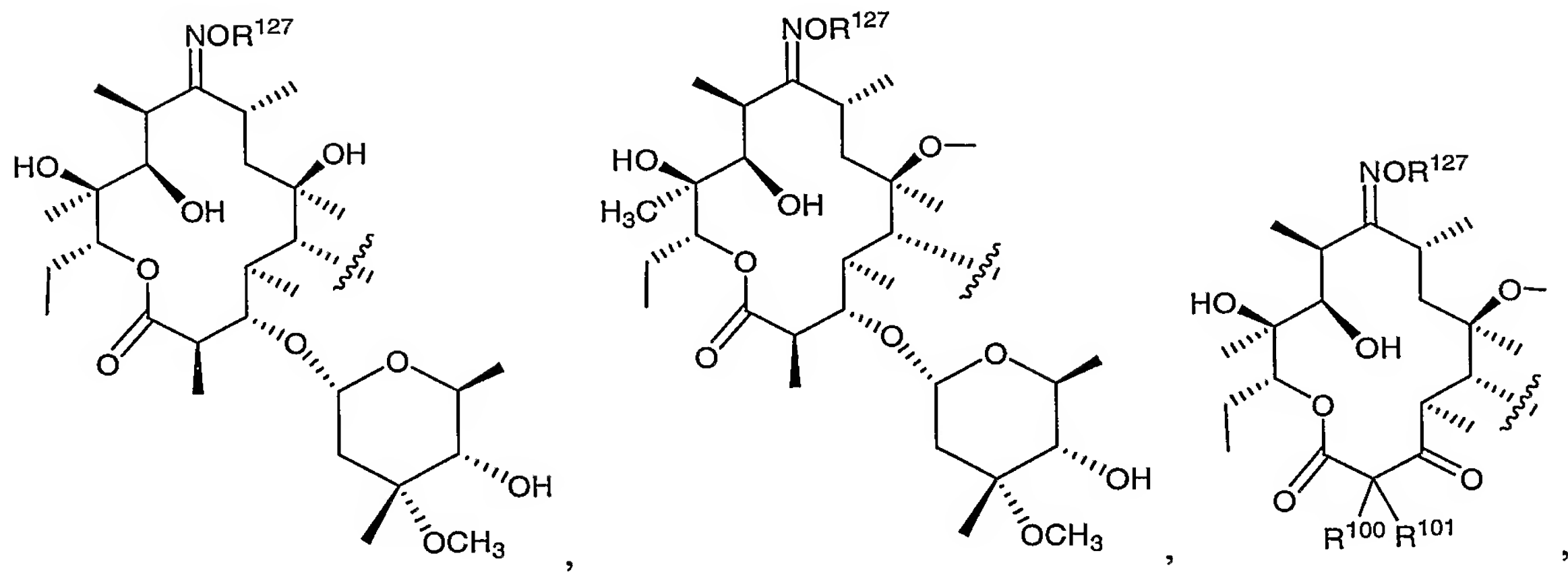
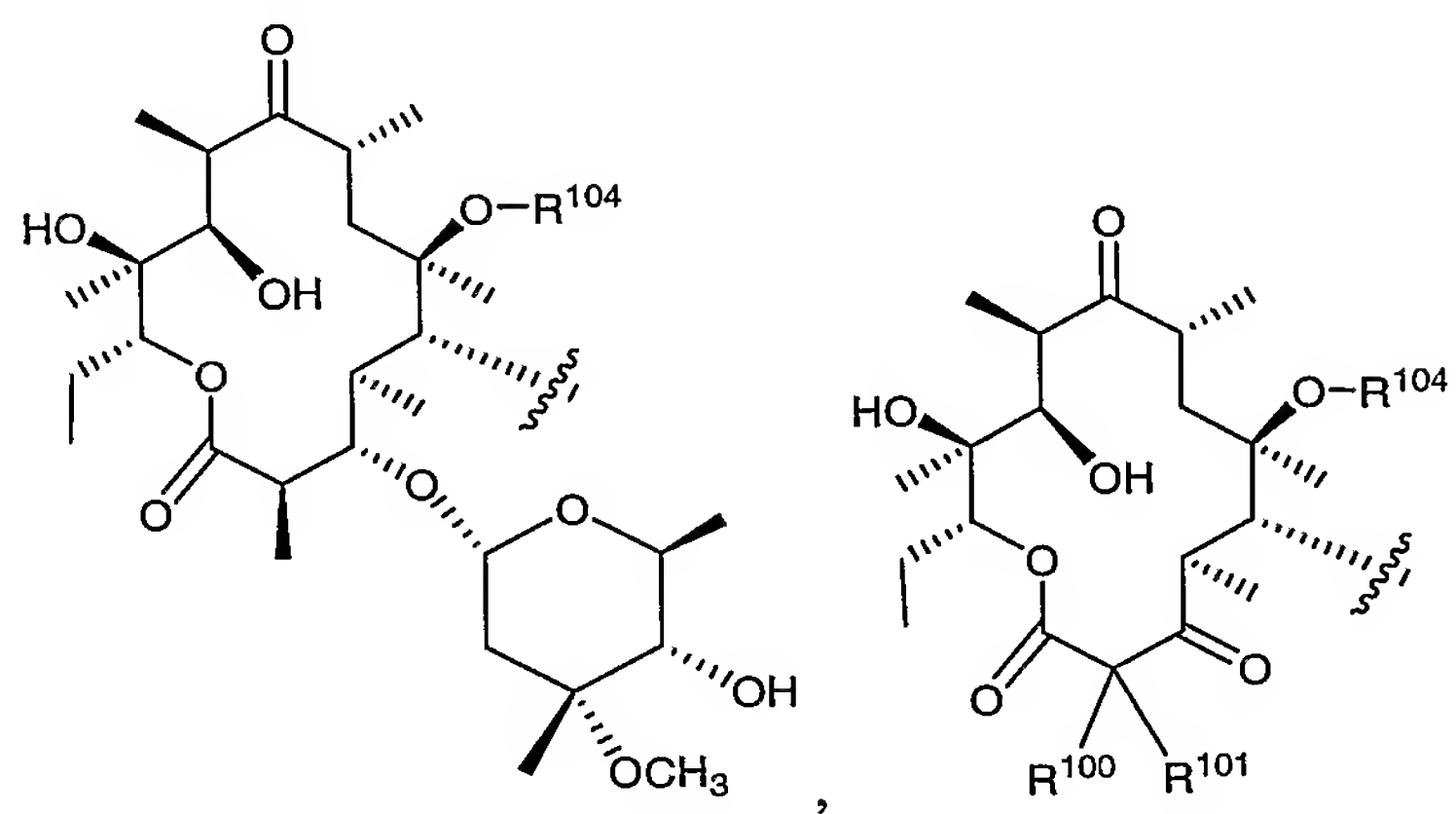
or an N-oxide pharmaceutically acceptable salt, ester, or prodrug thereof, wherein M, R^{100} , R^{101} , R^{104} , R^{105} , R^{106} , R^{107} , R^{108} , R^{109} , R^{110} , and R^{120} are as defined hereinabove.

Other embodiments of the foregoing compounds include those where T is a macrolide selected from the group consisting of:

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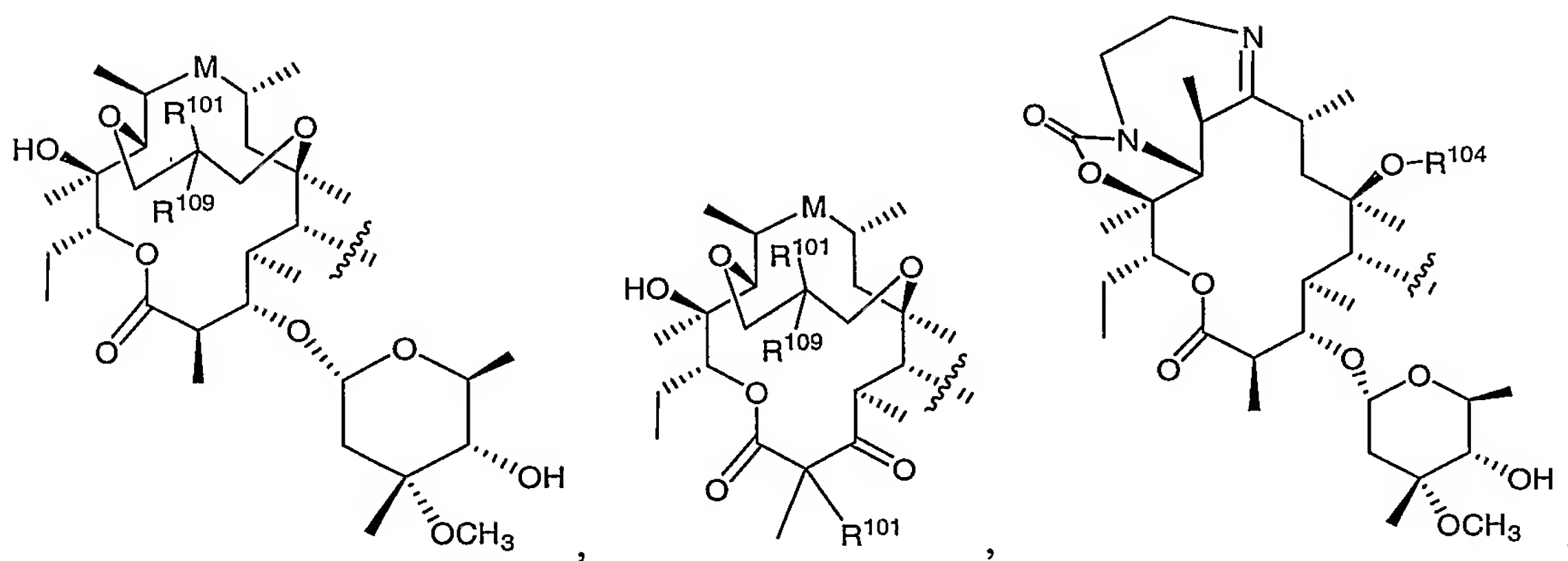
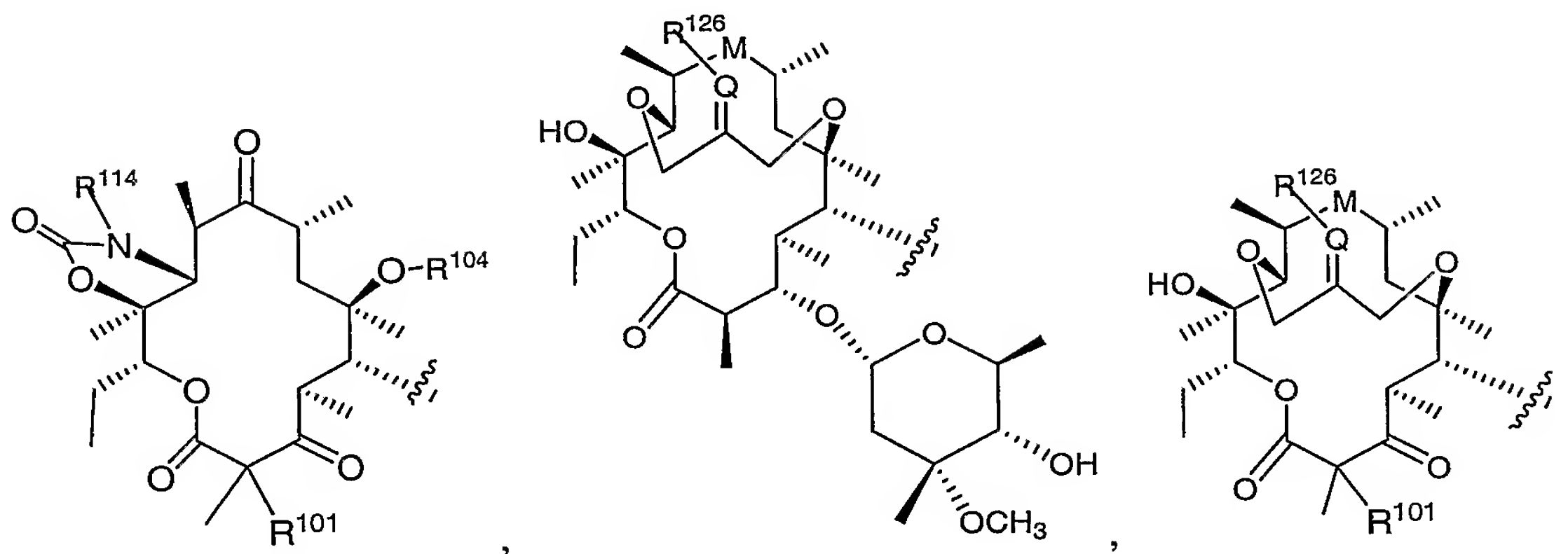
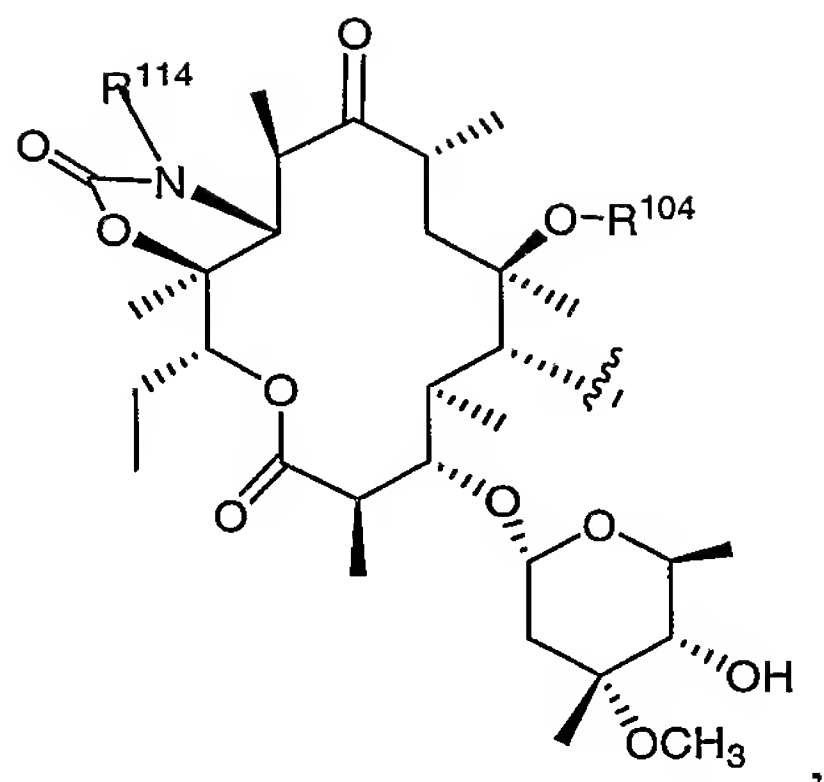


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- 40 -

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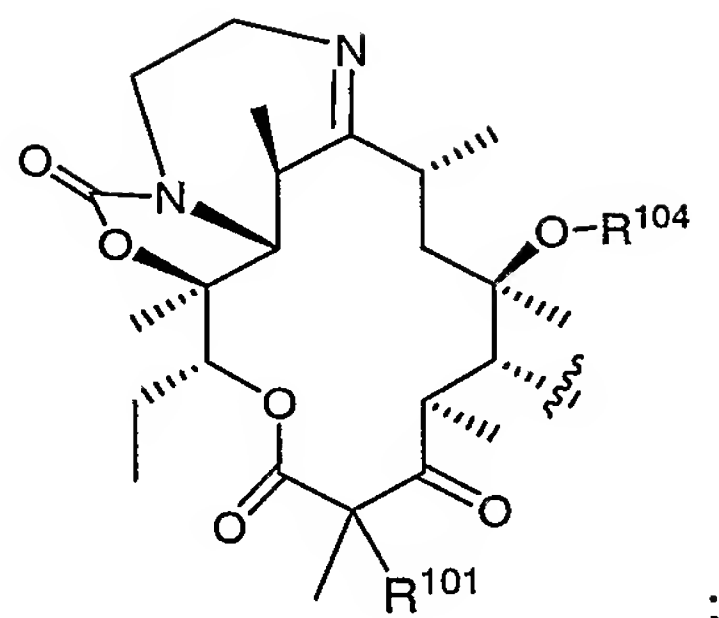


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- 41 -

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and

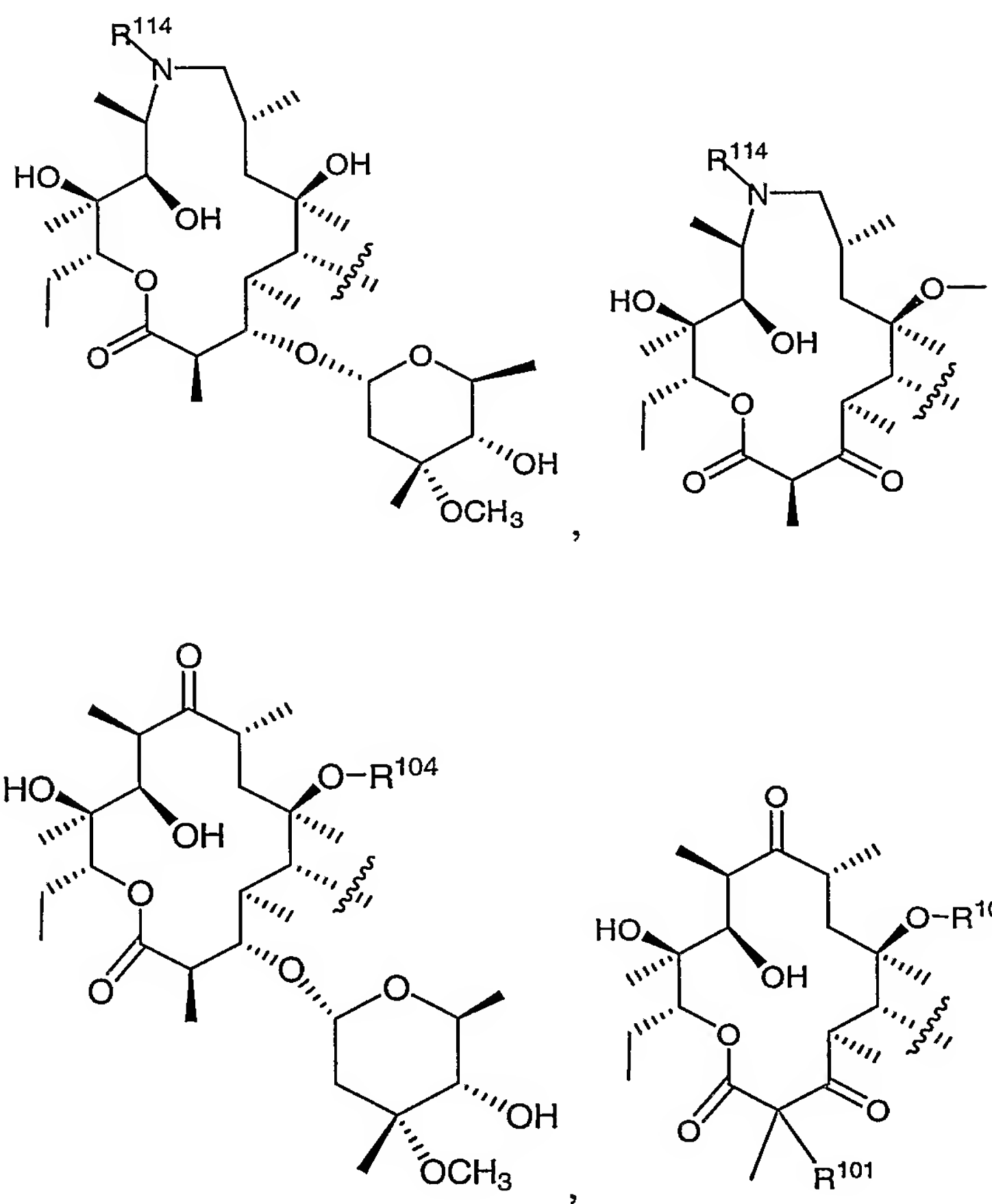


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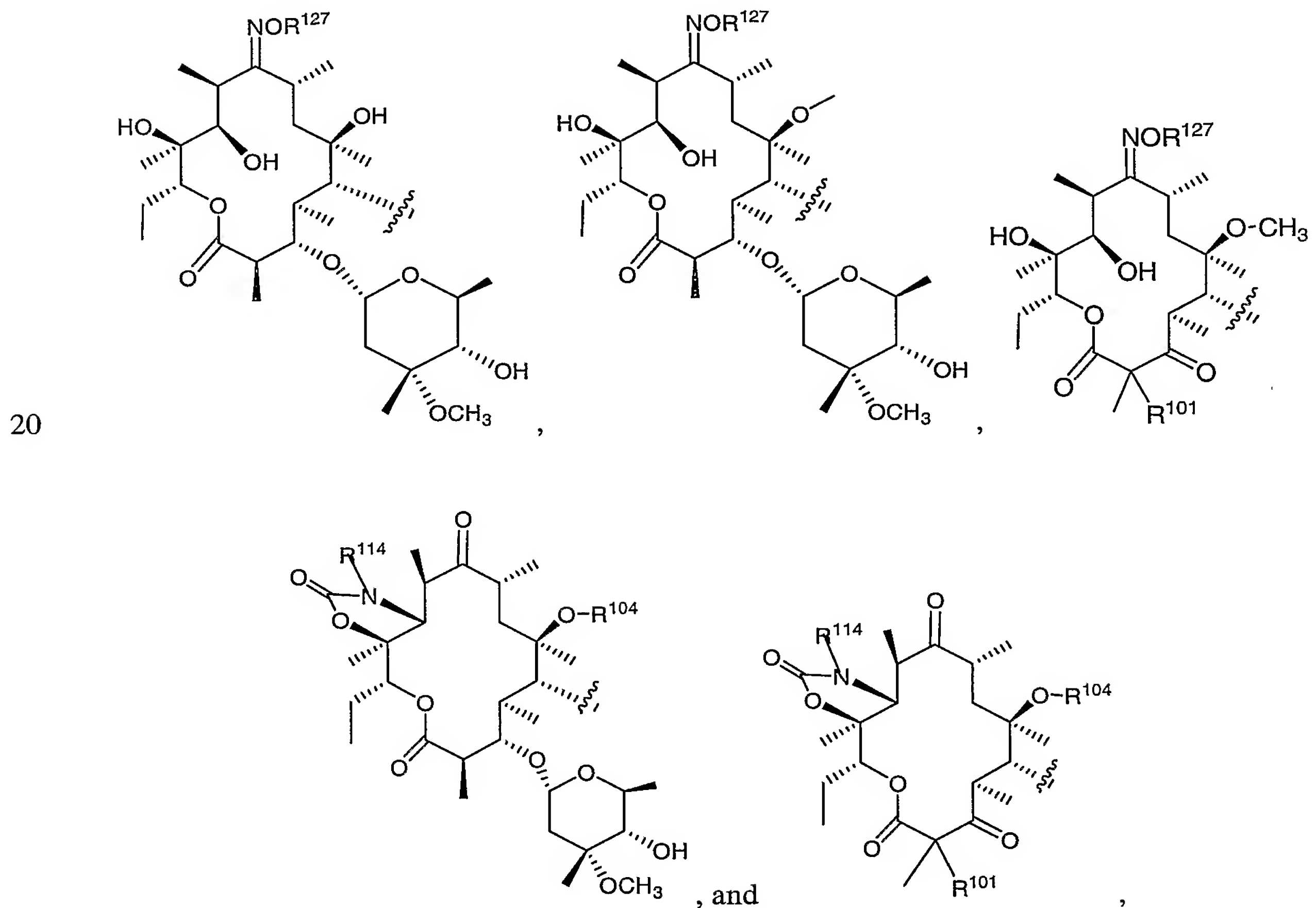
or an *N*-oxide pharmaceutically acceptable salt, ester, or prodrug thereof, wherein M, R¹⁰⁰, R¹⁰¹, R¹⁰², R¹⁰⁴, R¹⁰⁹, R¹¹⁴, R¹²⁶ and R¹²⁷ are as defined hereinabove.

25

Other embodiments of the foregoing compounds include those where T is a macrolide selected from the group consisting of:

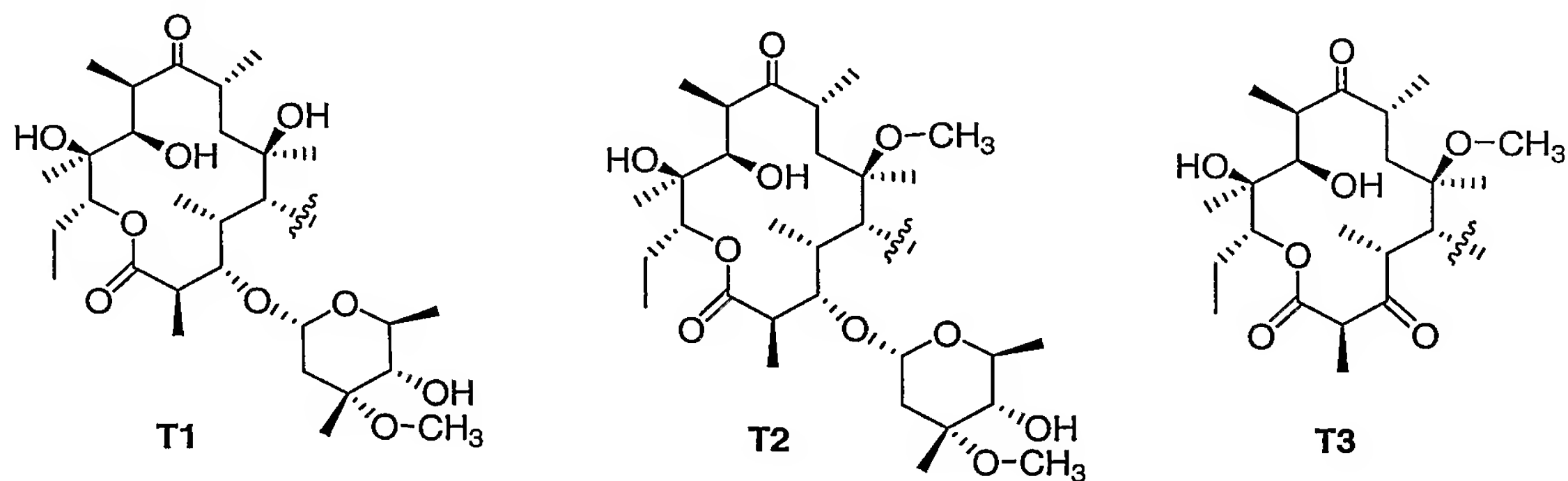


- 42 -

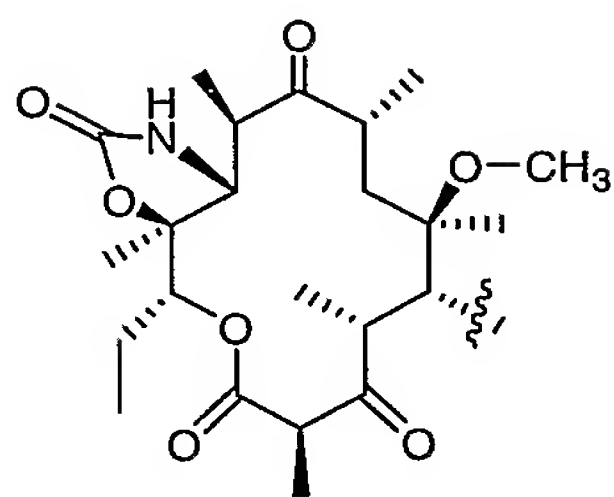


or an *N*-oxide pharmaceutically acceptable salt, ester, or prodrug thereof, wherein M, R¹, R²,
 25 R¹⁰⁴, R¹¹⁴, R¹⁰⁹ and R¹²⁷ are as defined hereinabove.

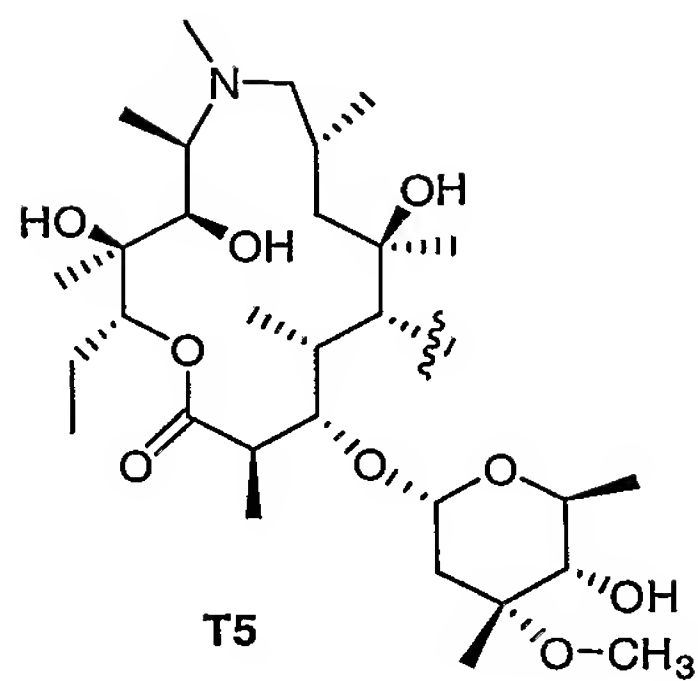
Other embodiments of the foregoing compounds include those where T is a macrolide selected from the group consisting of T1 through T33:



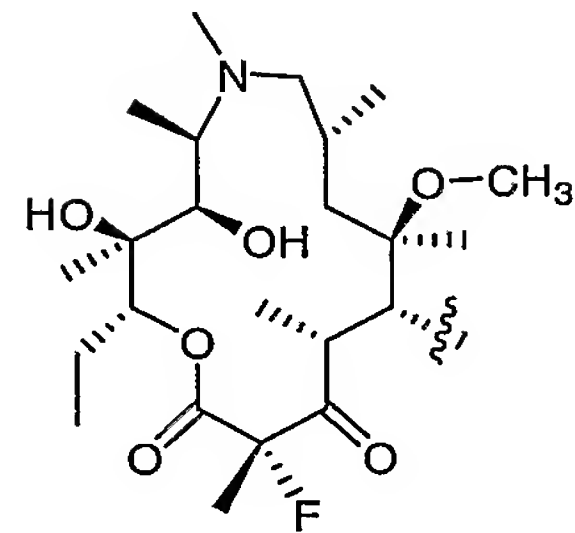
- 43 -



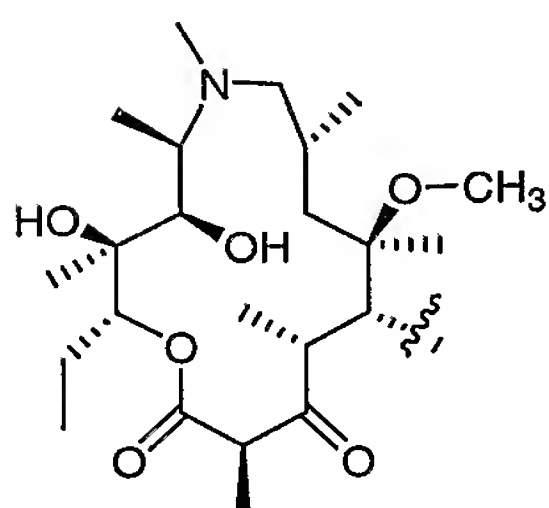
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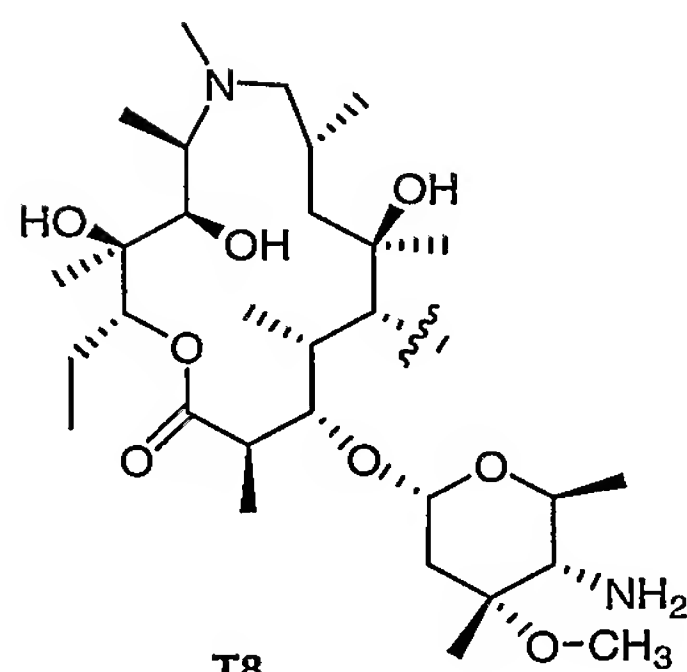
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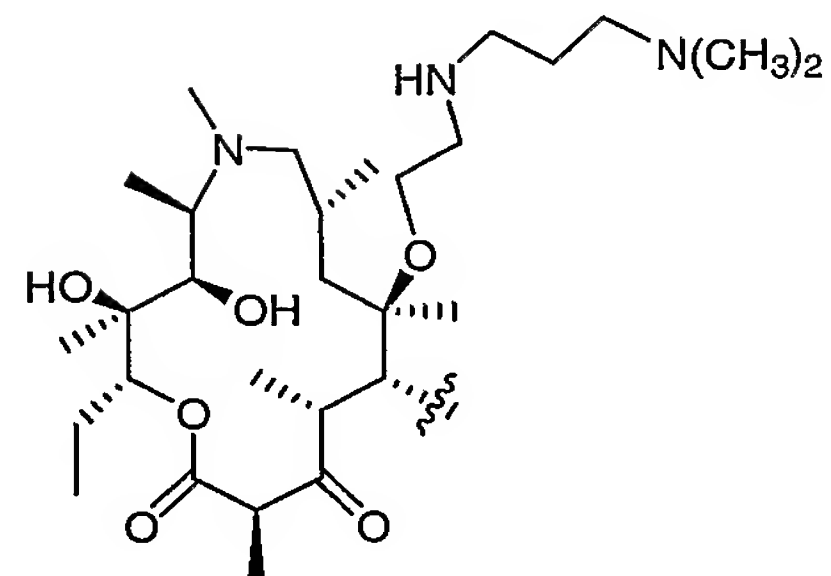
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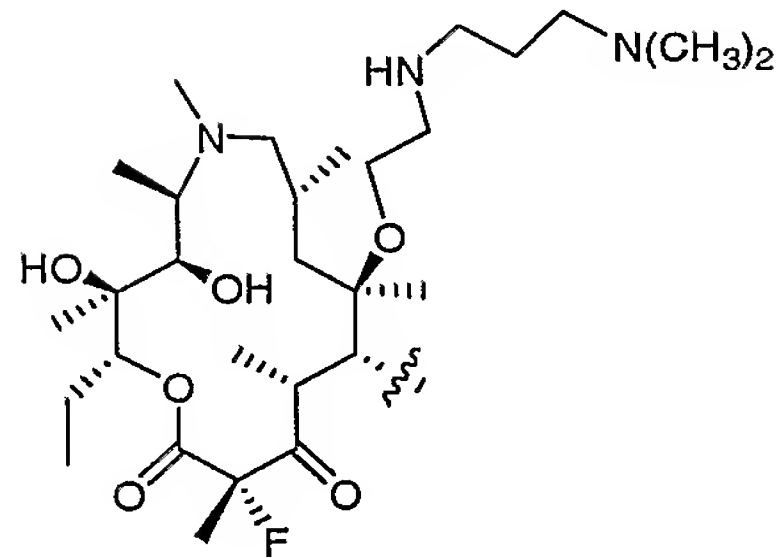
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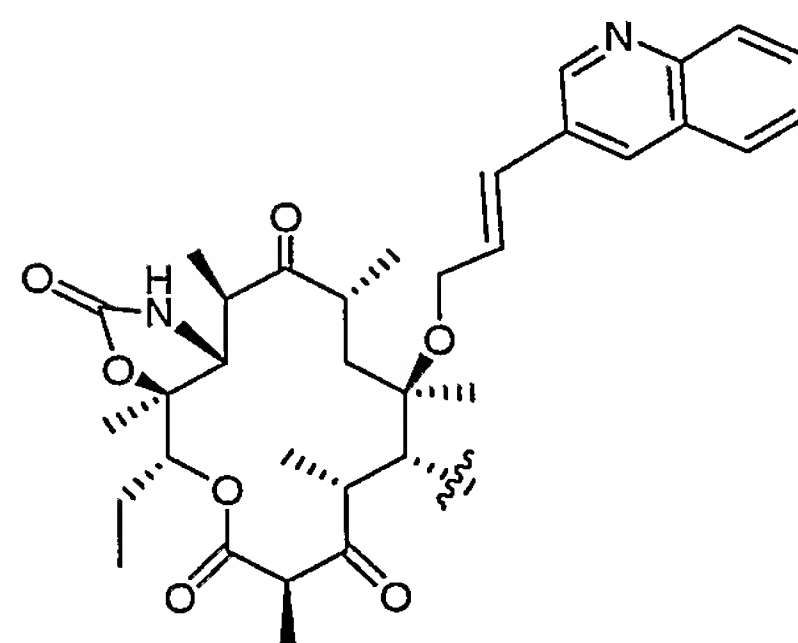
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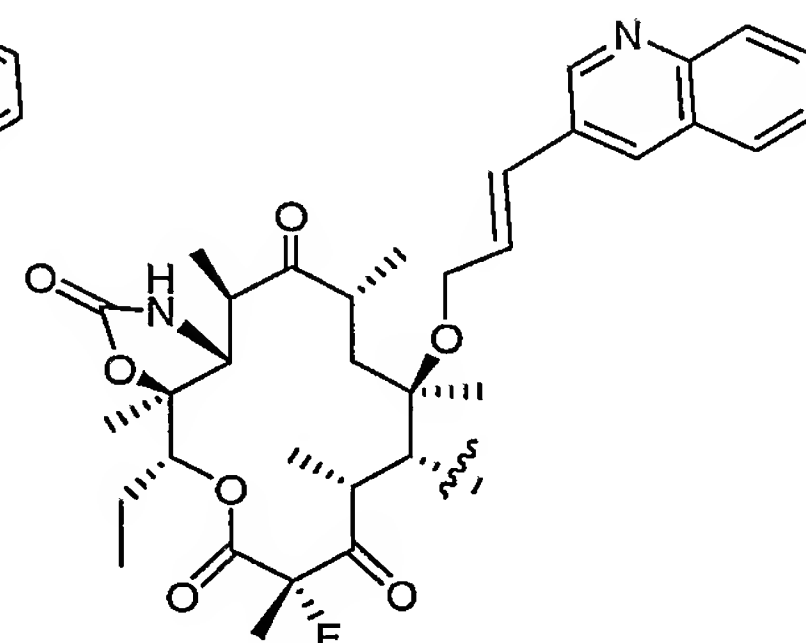
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T10



T11

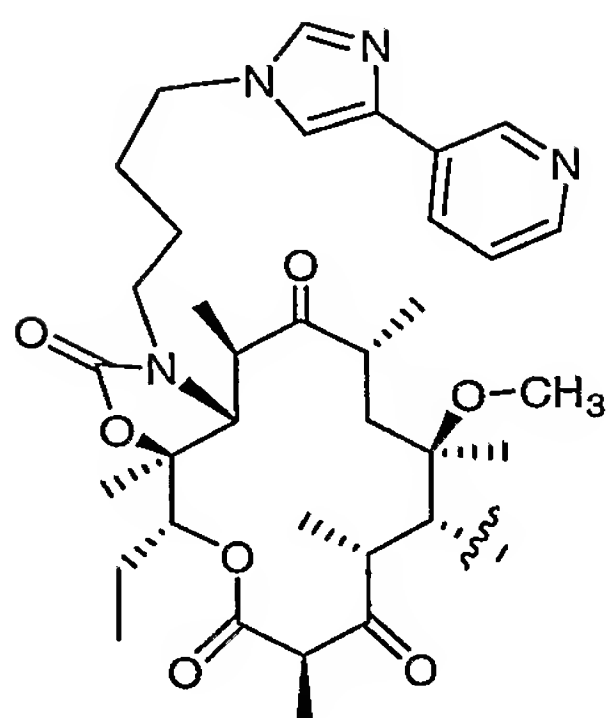


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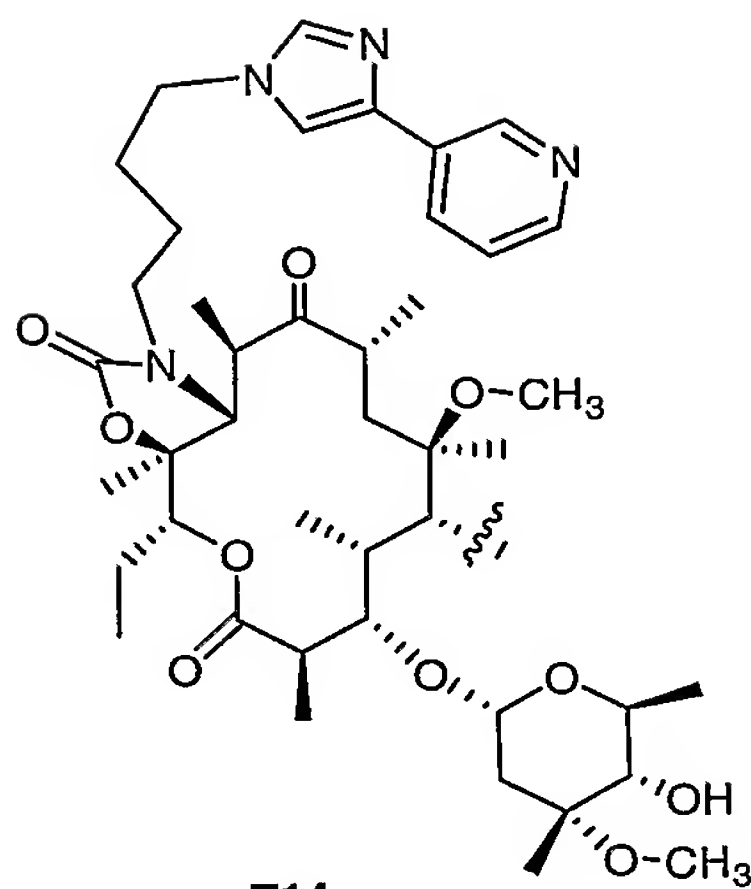
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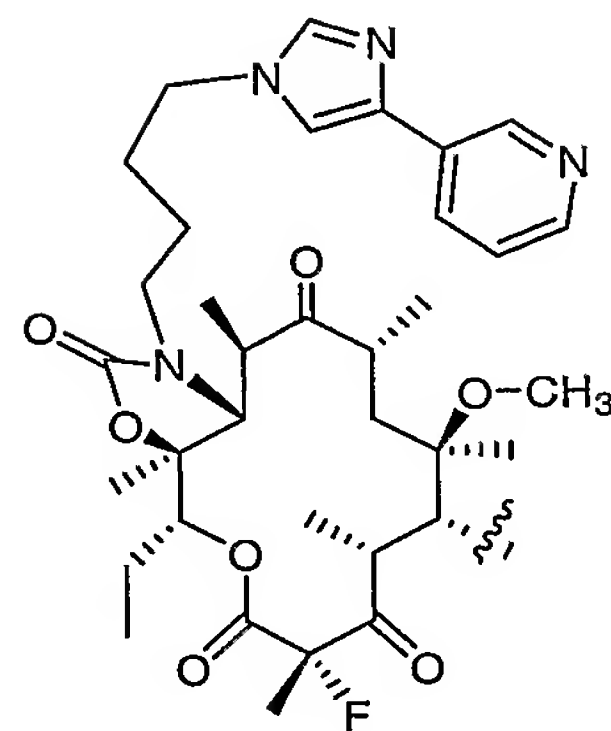
- 44 -



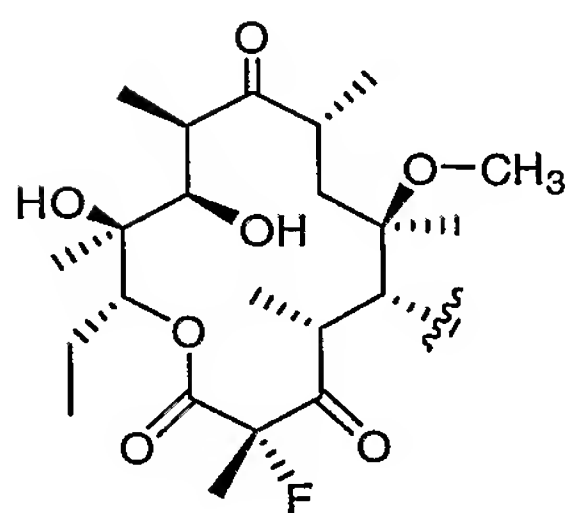
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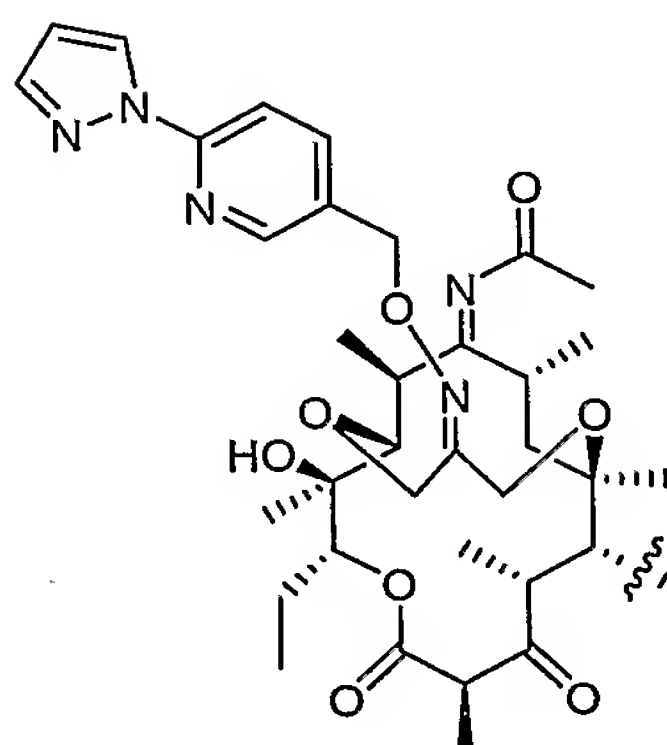
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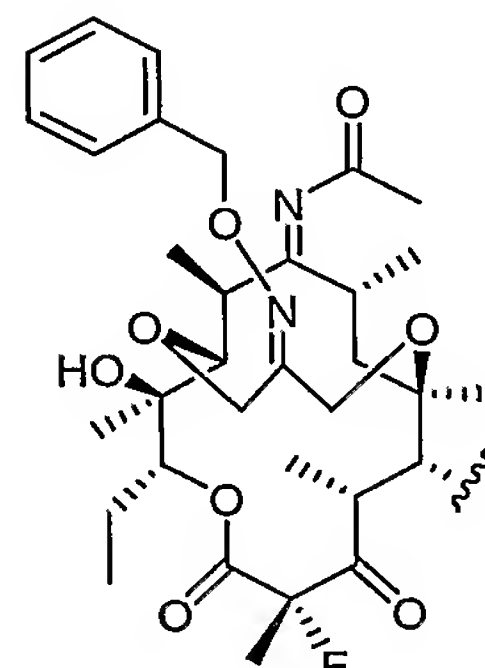
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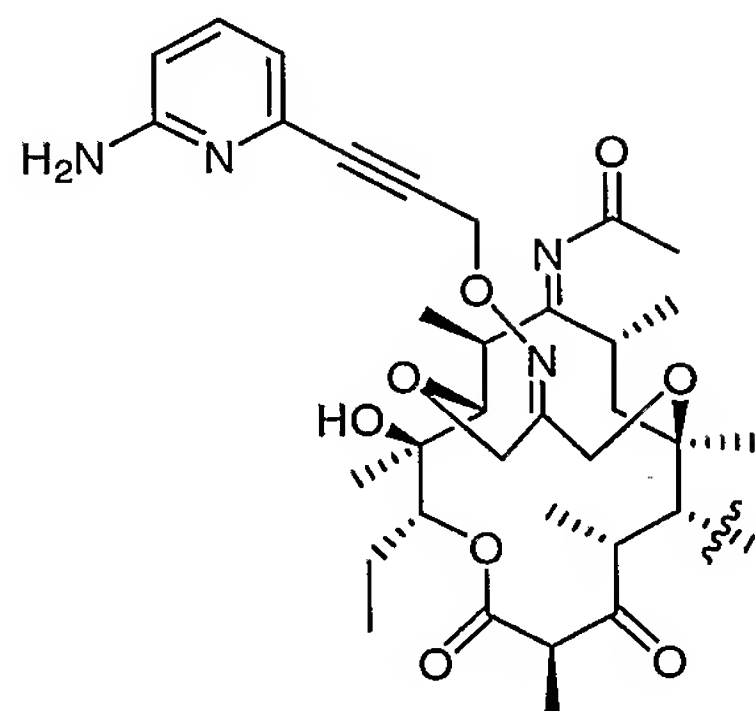
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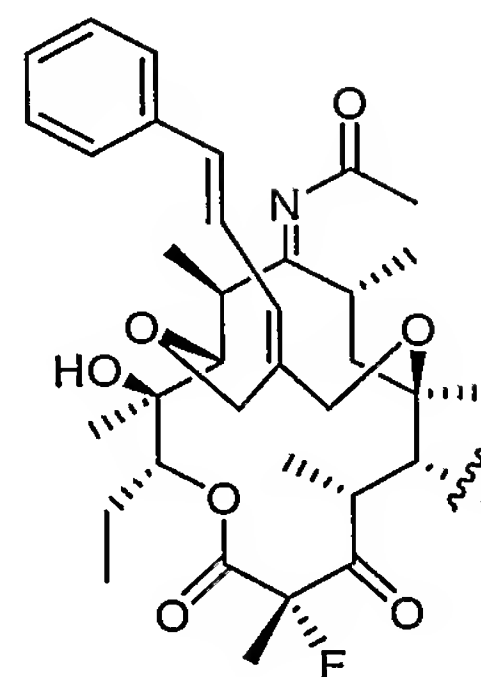
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T18



T19

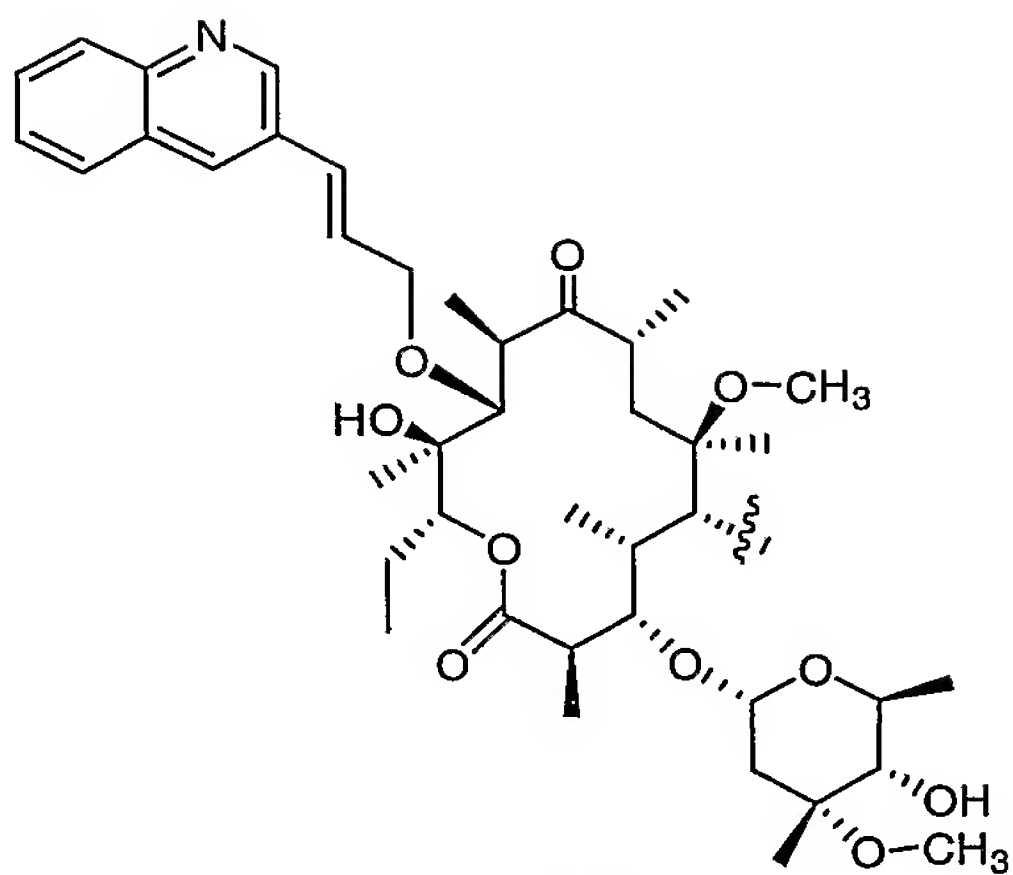


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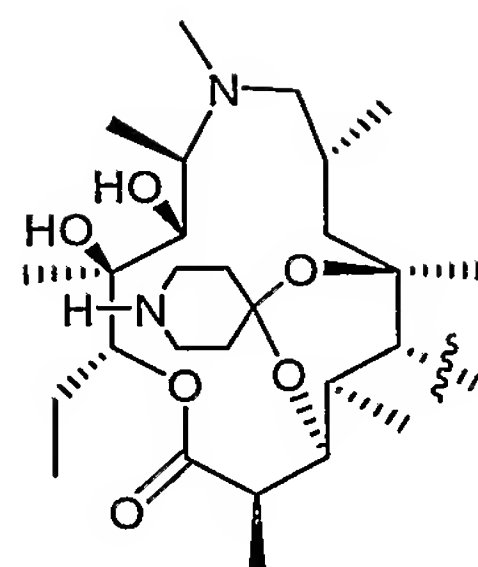
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- 45 -



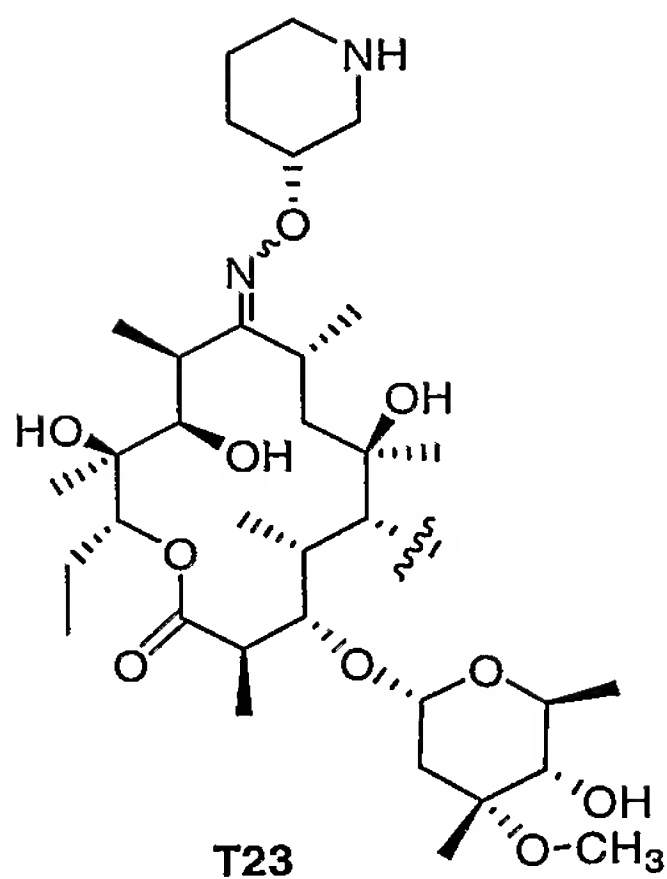
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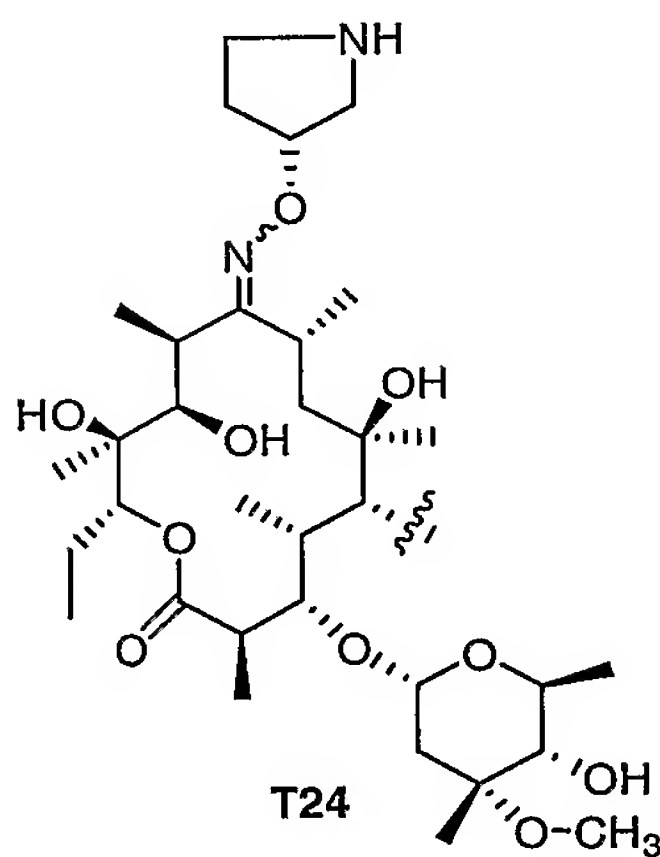
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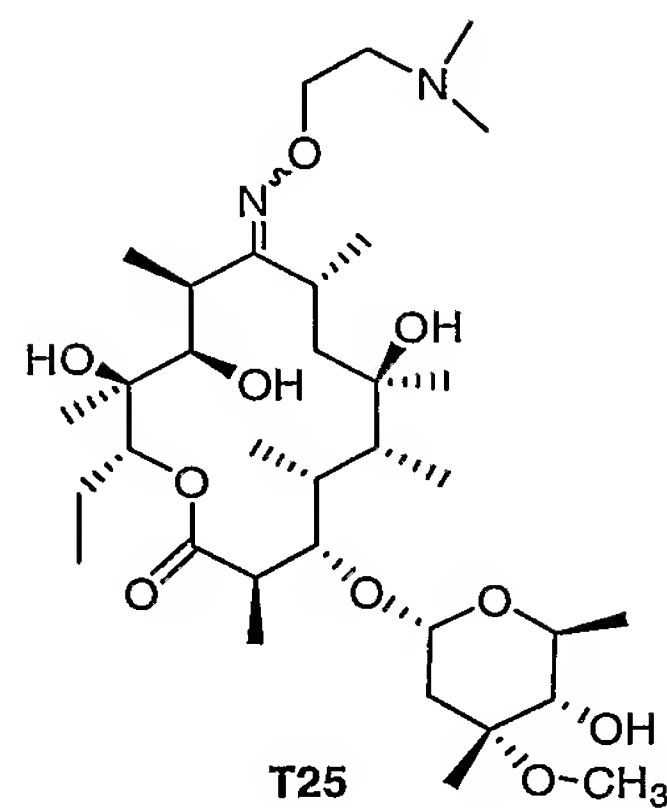
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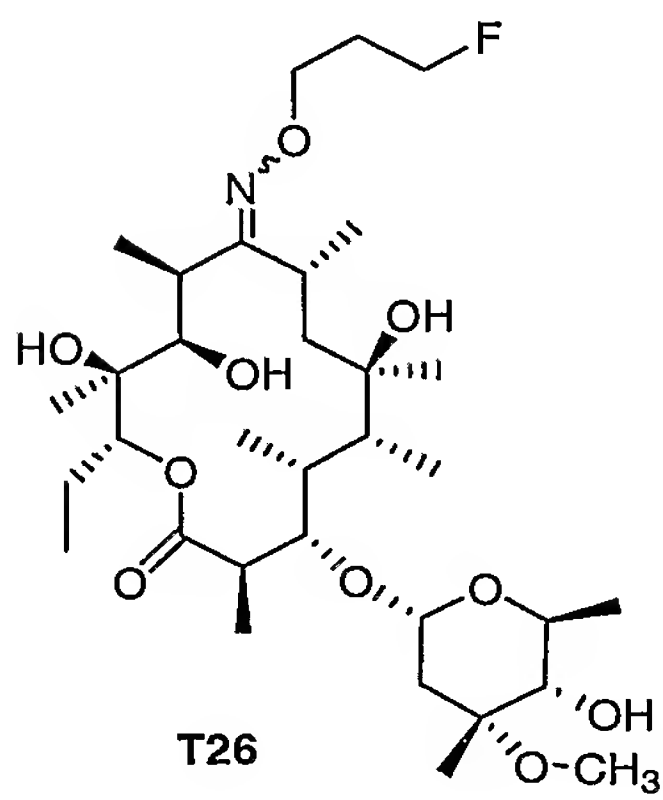
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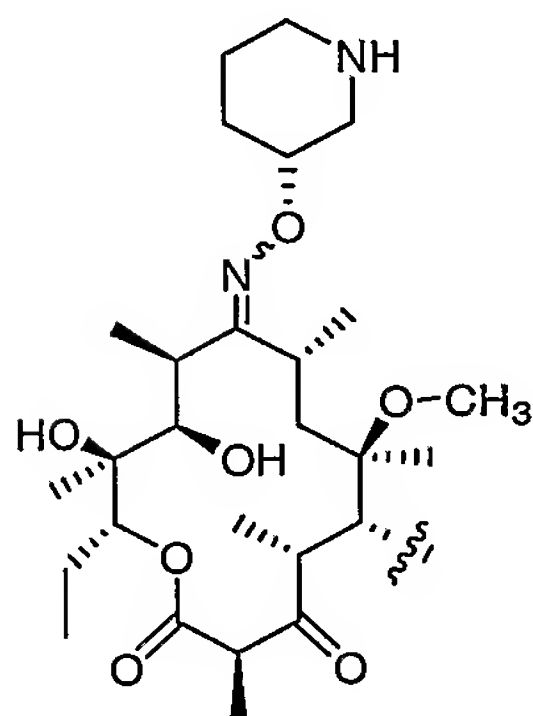
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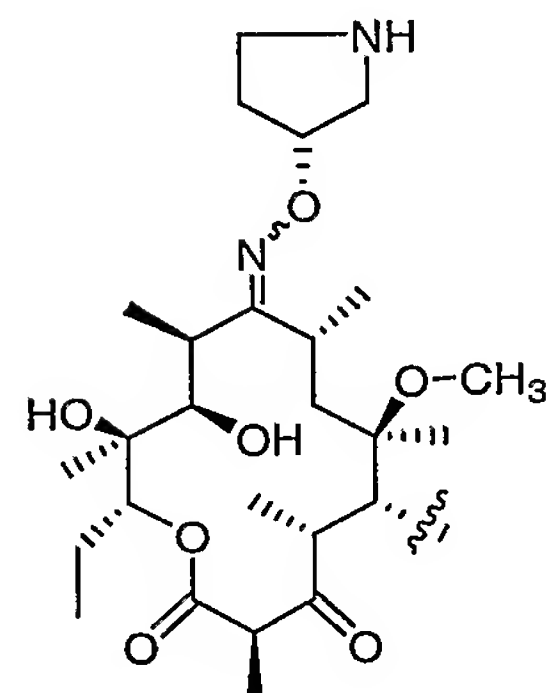
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T26

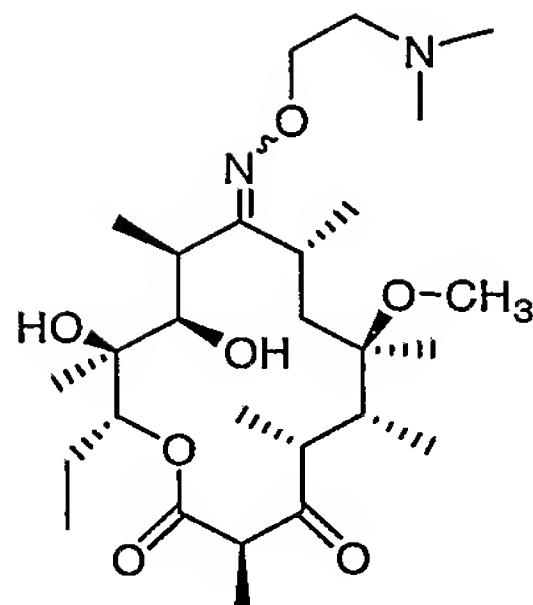


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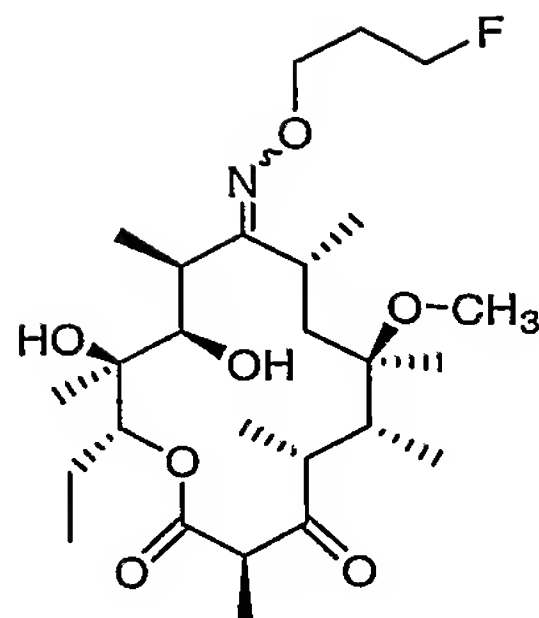


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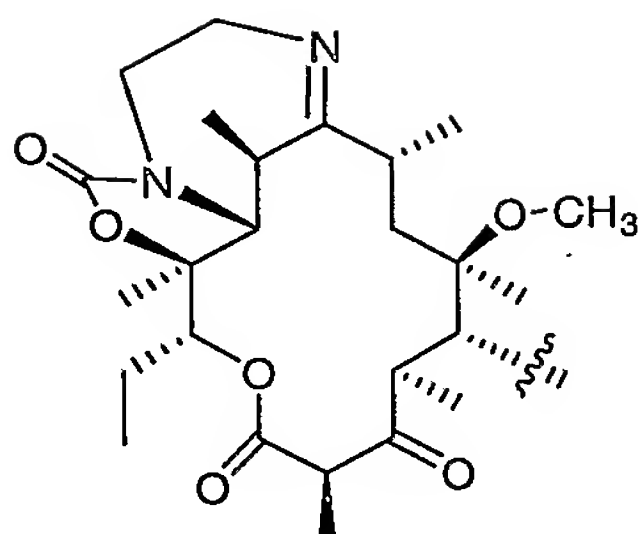
- 46 -



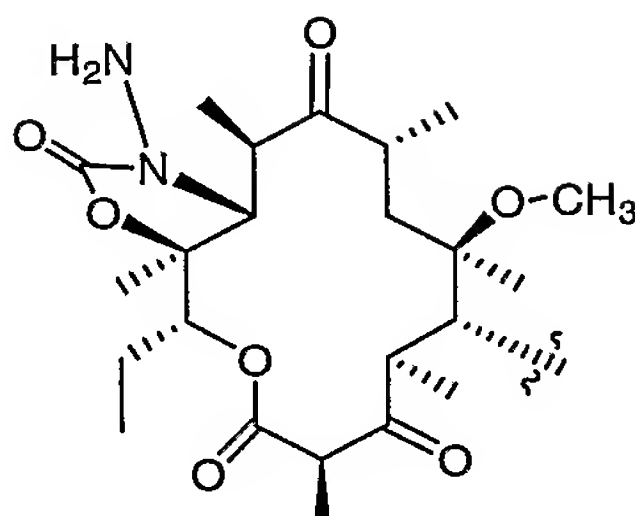
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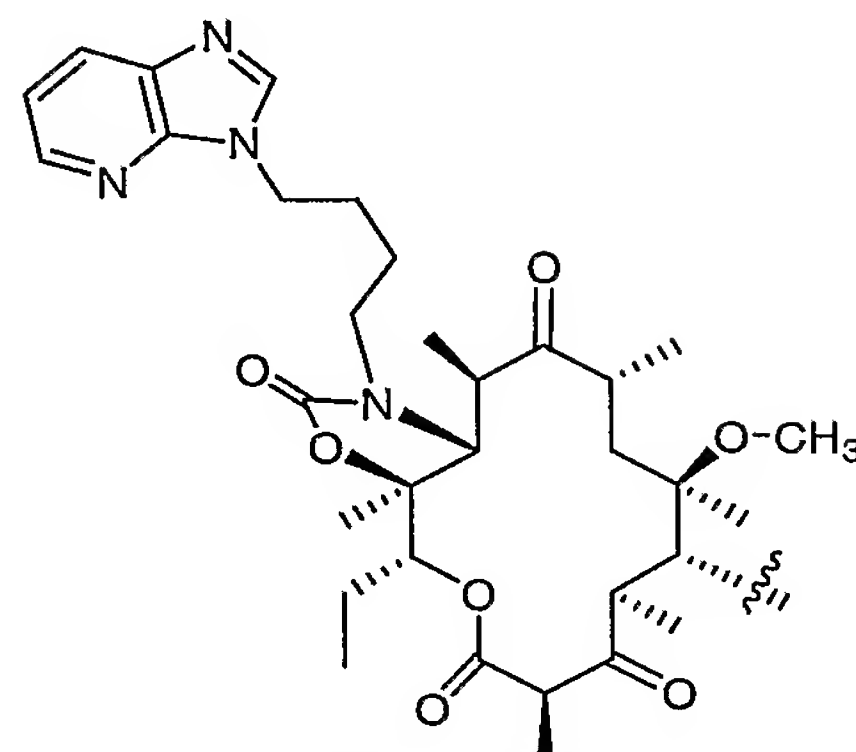
T30



T31



T32



T33

In another aspect, the invention provides a pharmaceutical composition comprising a
 25 therapeutically effective amount of one or more of the foregoing compounds and a
 pharmaceutically acceptable carrier. In yet another aspect, the invention provides a method for
 treating a microbial infection, a bacterial infection, a fungal infection, a parasitic disease, a
 proliferative disease, a viral infection, an inflammatory disease, or a gastrointestinal motility
 disorder in a mammal by administering effective amounts of the compounds of the invention or
 30 pharmaceutical compounds of the invention. In embodiments of this aspect, the compounds are
 administered orally, parentally, or topically. In still another aspect, the invention provides a
 medical device, for example, a medical stent, which contains or is coated with one or more of the
 foregoing compounds.

3. Synthesis of the Compounds of the Invention

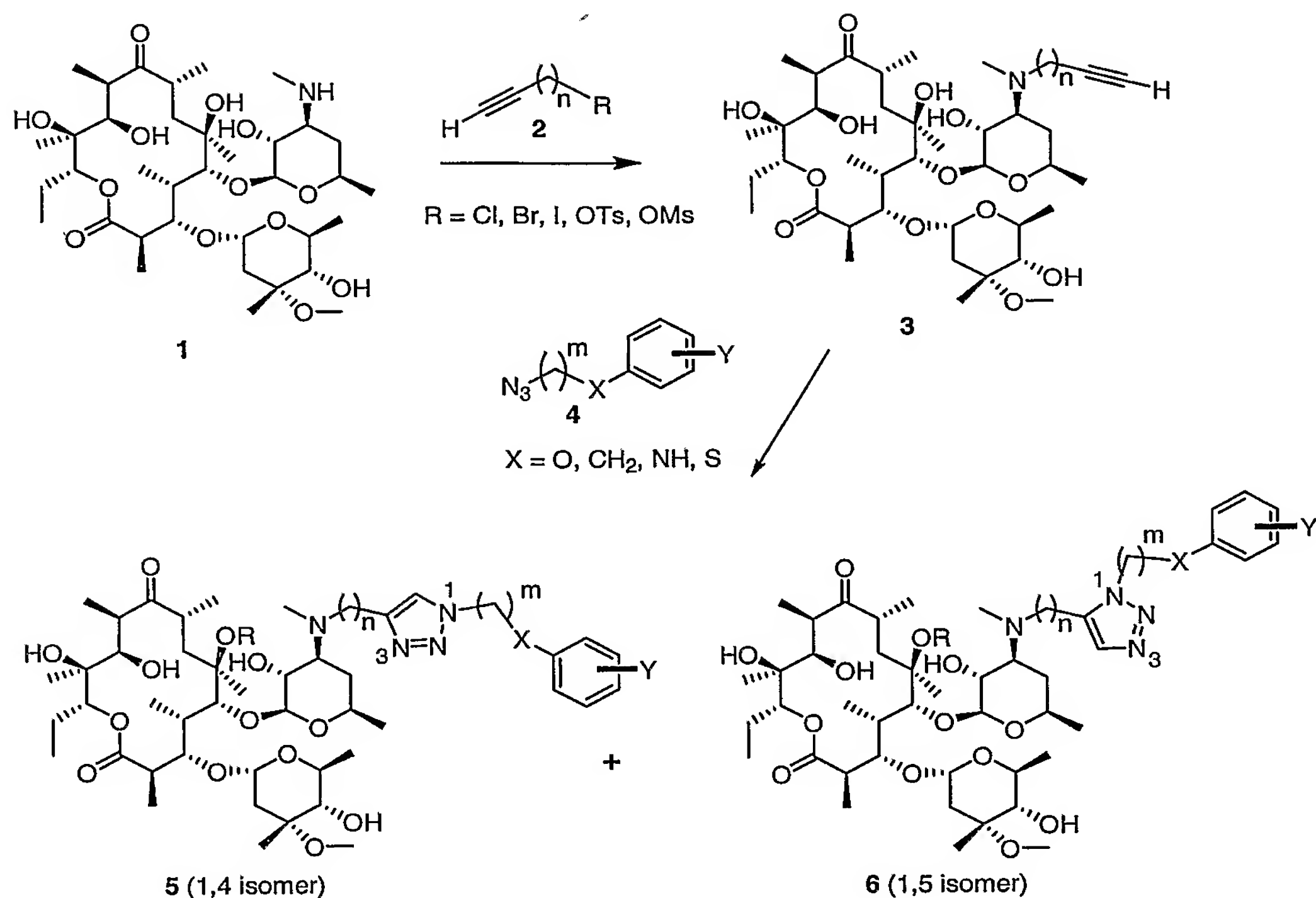
20 The invention provides methods for making the compounds of the invention. The following schemes depict exemplary chemistries available for synthesizing the compounds of the invention.

 The compound numbers, e.g., **1**, **2**, **3**, etc. used in this section 3 of the present application and entitled "**3. Synthesis of the Compounds of the Invention**", are for reference within this
25 section 3 only do not refer to and are not to be confused with any similarly numbered compounds in section 6 of the present application and entitled "**6. Examples**".

 Scheme 1 illustrates the synthesis of triazole compounds of type **5** and **6**. Erythromycin can be N-demethylated as described in the art (U.S. Patent No. 3,725,385; Flynn *et al.* (1954) J. AM. CHEM. SOC. 76: 3121; Ku *et al.* (1997) BIOORG. MED. CHEM. LETT. 7: 1203;
30 Stenmark *et al.* (2000) J. ORG. CHEM. 65: 3875) to afford secondary amine **1**. Alkylation of **1** with electrophiles of type **2** yields alkynes of type **3** containing an alkyl chain of appropriate length, generally between one and about four carbon atoms between the nitrogen atom and the alkyne group. Cycloaddition of azides of type **4** with alkynes **3** generates two regioisomeric triazole products. The reaction can be thermally catalyzed, or a number of catalysts could be
35 added to facilitate the reaction (such as, but not limited to, copper (I) iodide: see Tornøe, C.W. *et al.* (2002) J. ORG. CHEM. 67: 3057). The major isomer (for steric reasons) is the "anti" isomer **5**, a 1,4 disubstituted triazole. The minor component is the "syn" isomer **6**, a 1,5 disubstituted triazole.

Scheme 1

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It is to be understood that other macrolide compounds such as, but not limited to, azithromycin and clarithromycin, could be N-demethylated and serve as starting materials for the chemistry exemplified in Scheme 1. Target compounds derived from such alternate macrolide precursors are to be considered within the scope of the present invention.

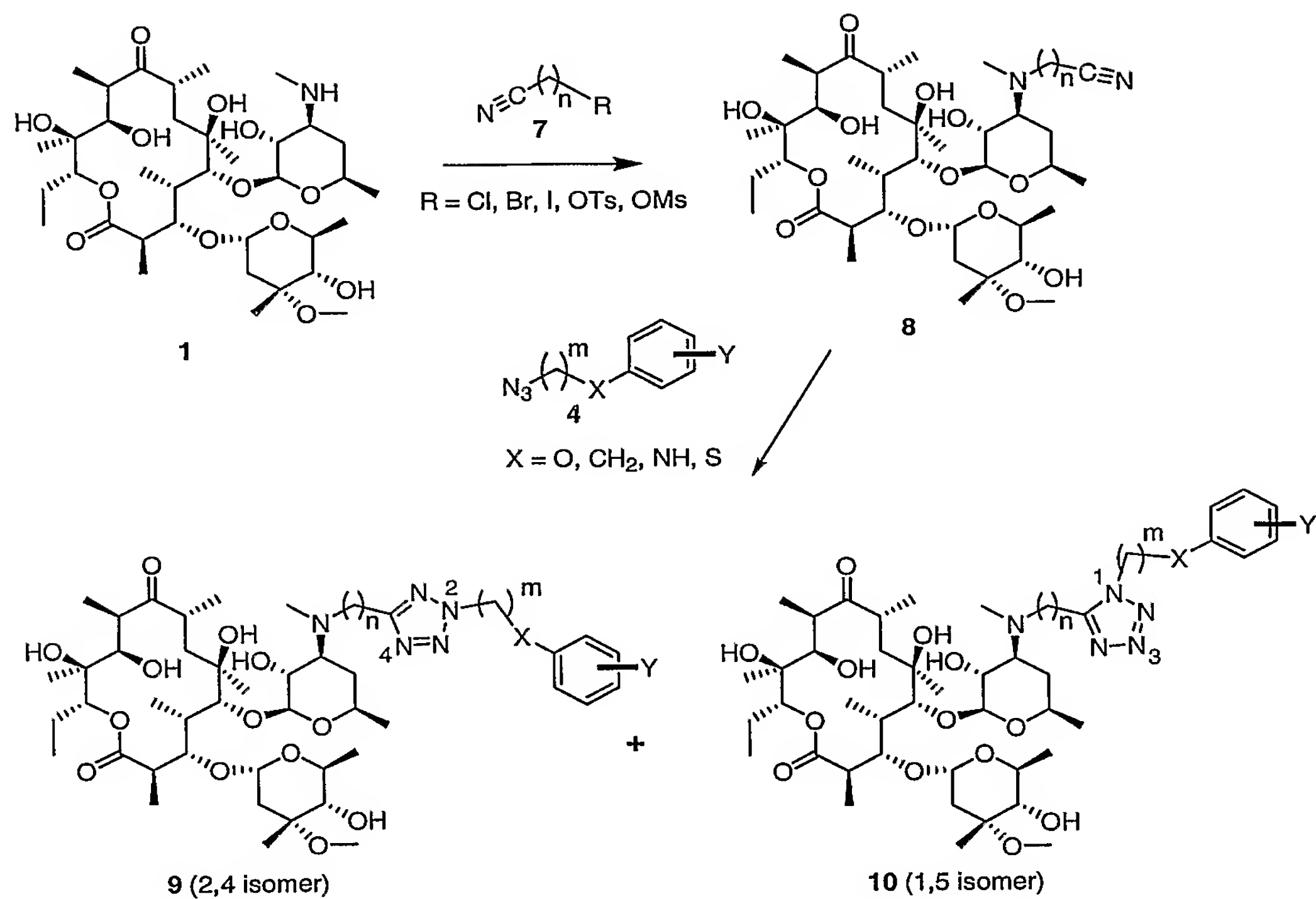
25

Scheme 2 illustrates the synthesis of exemplary tetrazole derivatives of the present invention. Amine **1** (or alternate macrolide amines) can be alkylated with nitrile-containing electrophiles of type **7** to afford macrolide nitrile intermediates of type **8**. Cycloaddition reactions of nitriles **8** with azides of type **4** may lead to two regioisomeric tetrazoles; the 2,4-disubstituted tetrazoles of type **9** (the expected major product), and the 1,5 isomers of type **10**.

30

Scheme 2

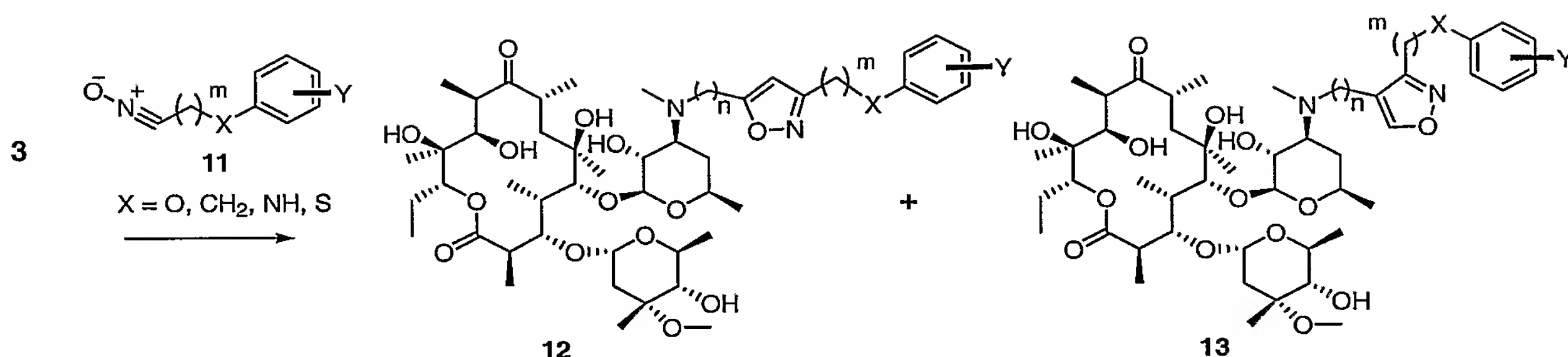
- 49 -



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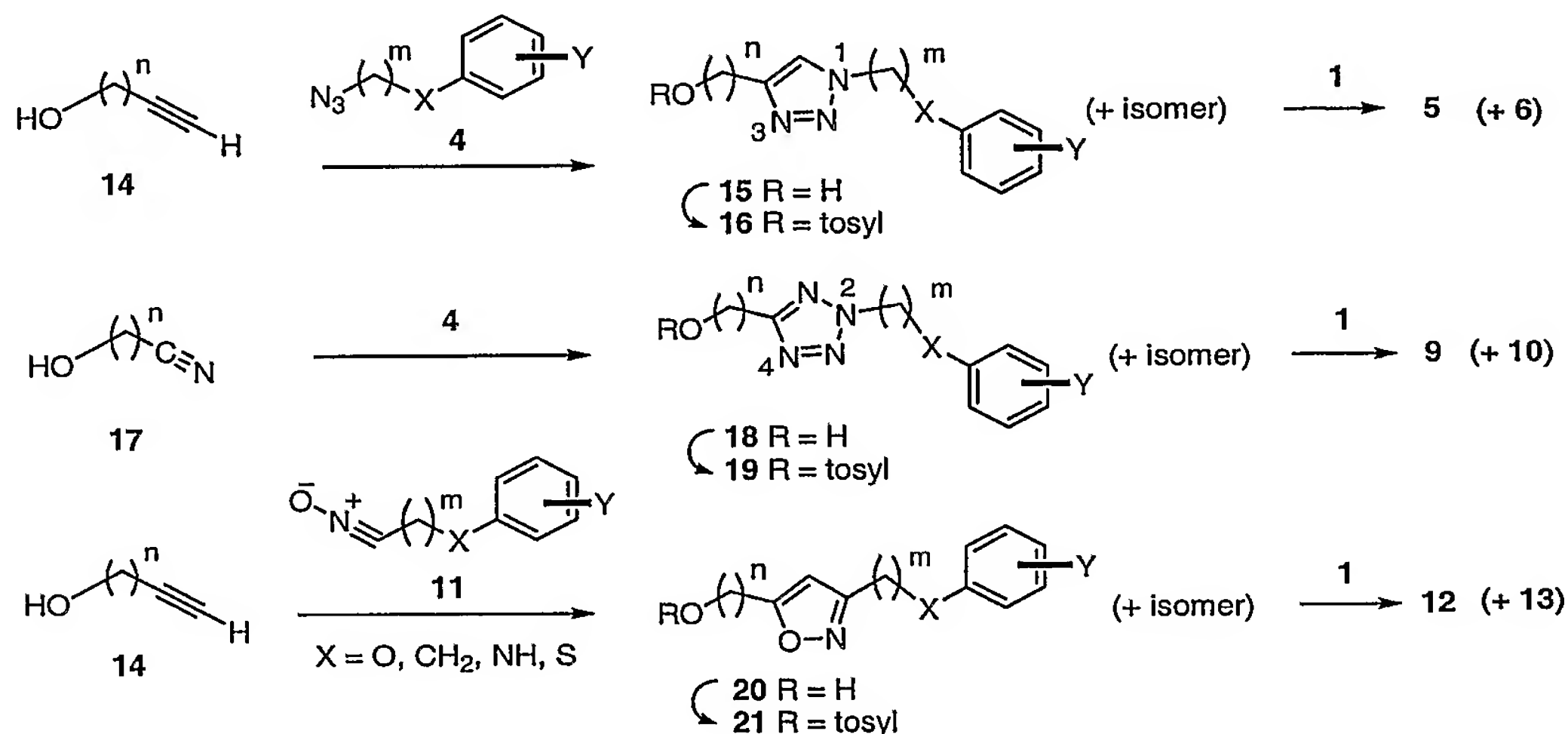
Scheme 3 depicts the synthesis of isoxazole derivatives of the present invention. Alkynes **3** can be treated with nitrile oxides of type **11** to afford regioisomeric cycloadducts **12** and **13**. The major isomer should again be the “anti” derivative **12** based on steric factors.

20 Scheme 3



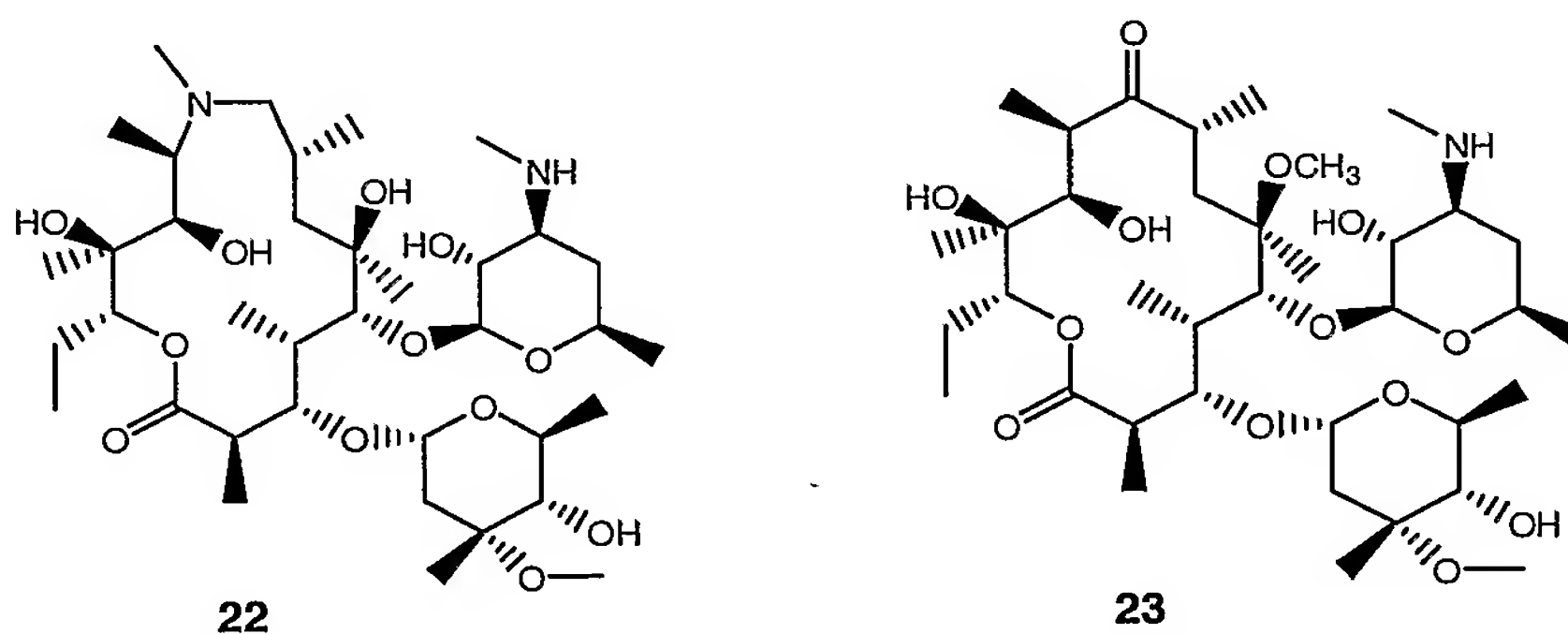
An alternate approach to derivatives of type **5**, **6**, **9**, **10**, **12**, and **13** is illustrated by Scheme 4. Acetylenic alcohols of type **14** can be treated with azides **4** to yield intermediate alcohol **15** (along with a minor amount of the regioisomeric triazole). Tosylation of **15** will provide tosylates **16** which can serve as alkylating agents for macrolide amines of type **1** to afford targets **5** (and its isomer **6**). (It will be appreciated that other sulfonate derivatives or halides could be formed from intermediate alcohol **15**, and these would be useful as electrophiles for the alkylation of macrolide amines such as **1** to afford compounds of the invention.) Hydroxyalkyl nitriles of type **17** (where n is not equal to 1) can undergo cycloaddition with azides **4** to afford tetrazole intermediate **18** (along with a minor amount of the regioisomeric tetrazole). Tosylation of **18** to give **19** can again be followed by alkylation with amines of type **1** to yield derivative **9** (and its isomer **10**). In an analogous fashion, acetylenes **14** can be converted to isoxazoles **20** (and its isomer). An appropriate electrophile derived from **20** can then alkylate amines **1** to afford target **12** (and its isomer **13**).

35 Scheme 4



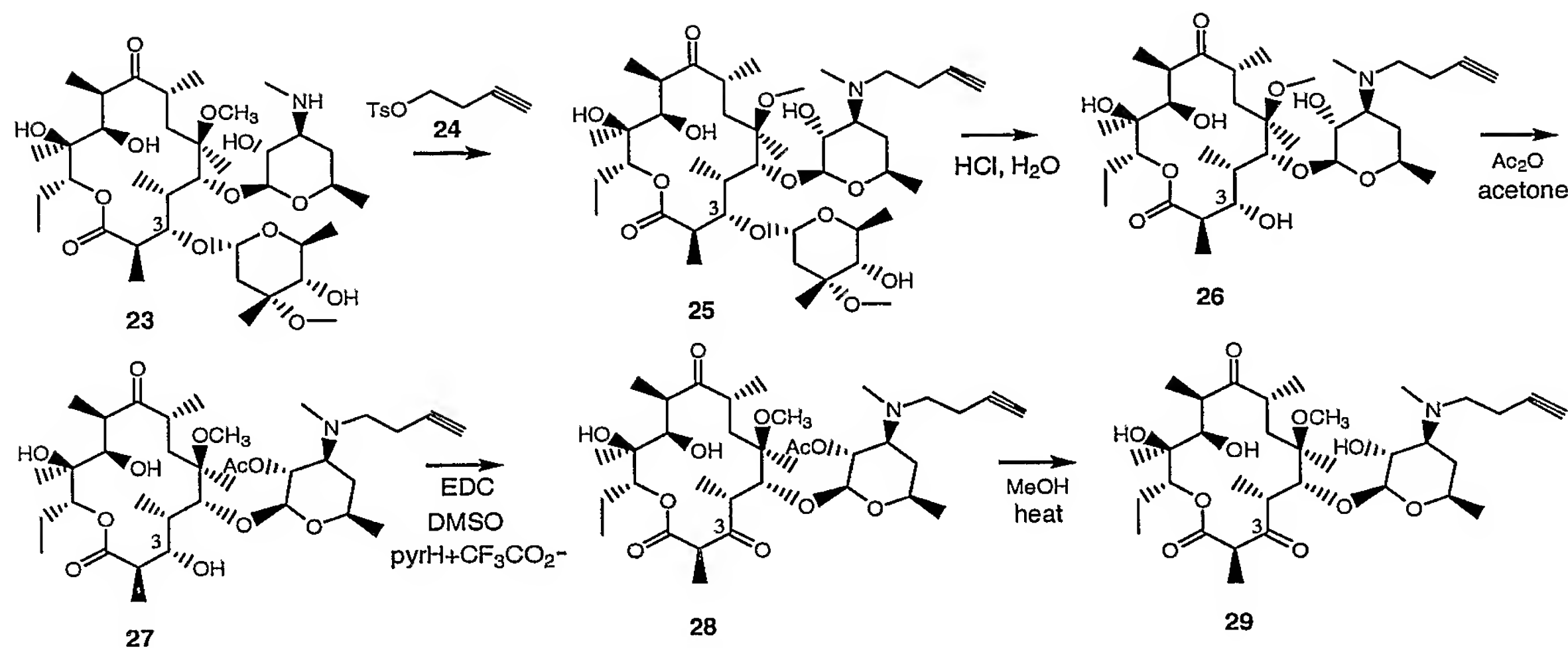
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Other starting materials for the synthesis of compounds of the present invention are readily synthesizable. For example, des-methyl macrolide amines **22** and **23** can be prepared from azithromycin and clarithromycin respectively, using the same procedure for the synthesis of **1** from erythromycin. Ketolide derivatives (C-3 keto compounds synthesized from macrolides) of the present invention can be prepared by chemistry such as that shown in Scheme 5. Clarithromycin-derived amine **23** is alkylated with tosylate **24** to afford alkyne **25**. The cladinose sugar at C-3 is hydrolyzed to afford the C-3 hydroxy intermediate **26**, which is then selectively acetylated on the hydroxyl of the aminosaccharide group to yield **27**. Oxidation of **27** yields C-3 keto derivative **28** which is then deacylated to provide alkyne **29**. Alkyne **29** can be exposed to the chemistry of Schemes 1 and 3 above to deliver triazole and isoxazole compounds of the present invention that have C-3 keto clarithromycin-derived structures. It will be understood that alkylation of **23** with electrophiles of type **7**, and then exposure of the product nitriles to the chemistry shown in Schemes 5 and 2, will yield tetrazoles that have C-3 keto clarithromycin-derived structures. Additionally, C-3 keto azithromycin and erythromycin intermediates could be prepared from **1** and **22** using the chemistry of Scheme 5, and subsequently serve as starting materials for compounds of the present invention.



Scheme 5

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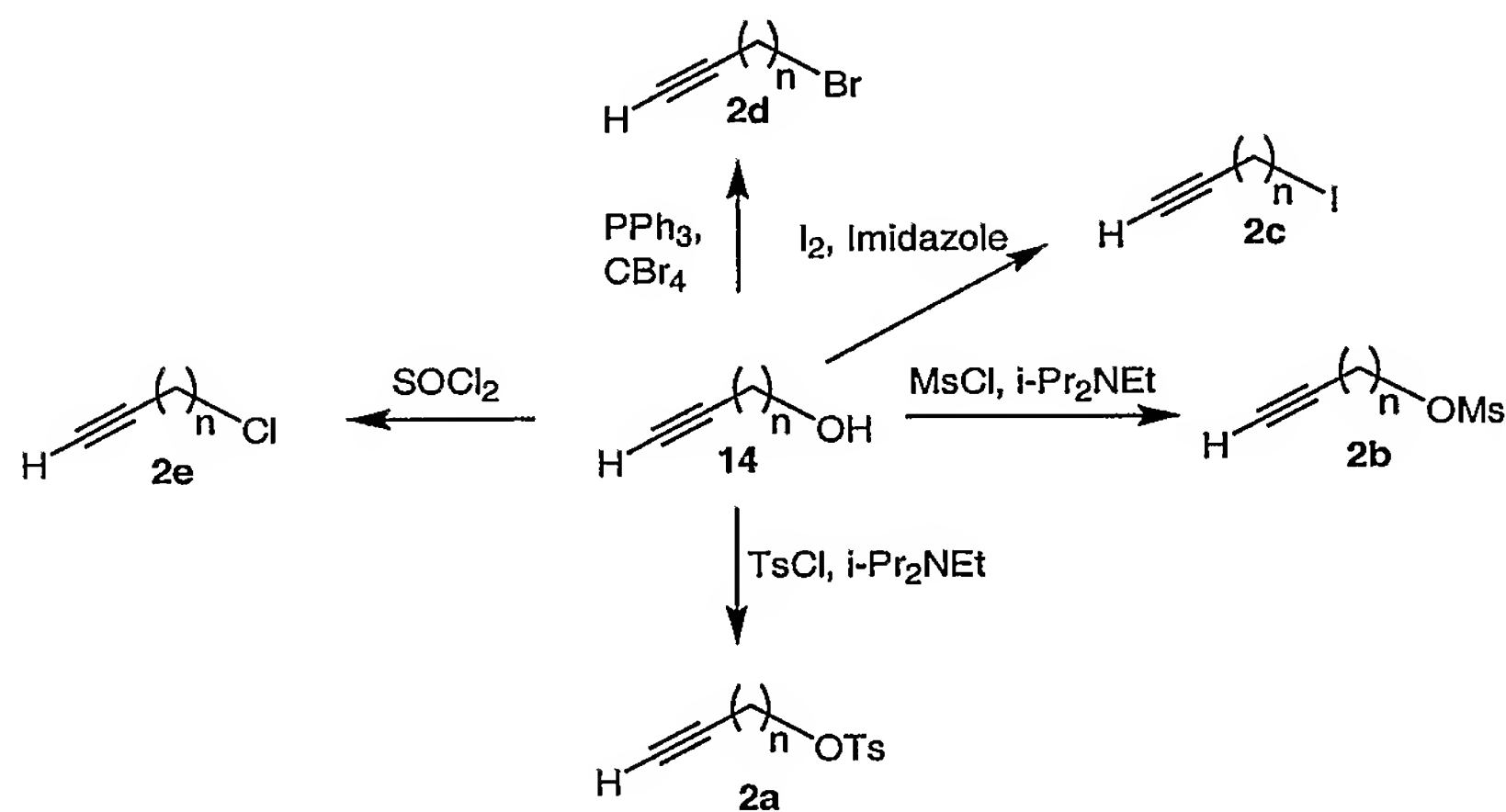


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Acetylenes of type **2**, used to synthesize the variable length alkyl chains in the compounds, can be derived from commercially available haloalkyl acetylenes such as propargyl bromide, or they can be readily synthesized from available hydroxyalkyl acetylenes using chemistry well known in the art. Scheme 6 illustrates how they can be synthesized from available hydroxyalkyl acetylenes of type **14** using simple chemistry well known in the art.

25

Scheme 6

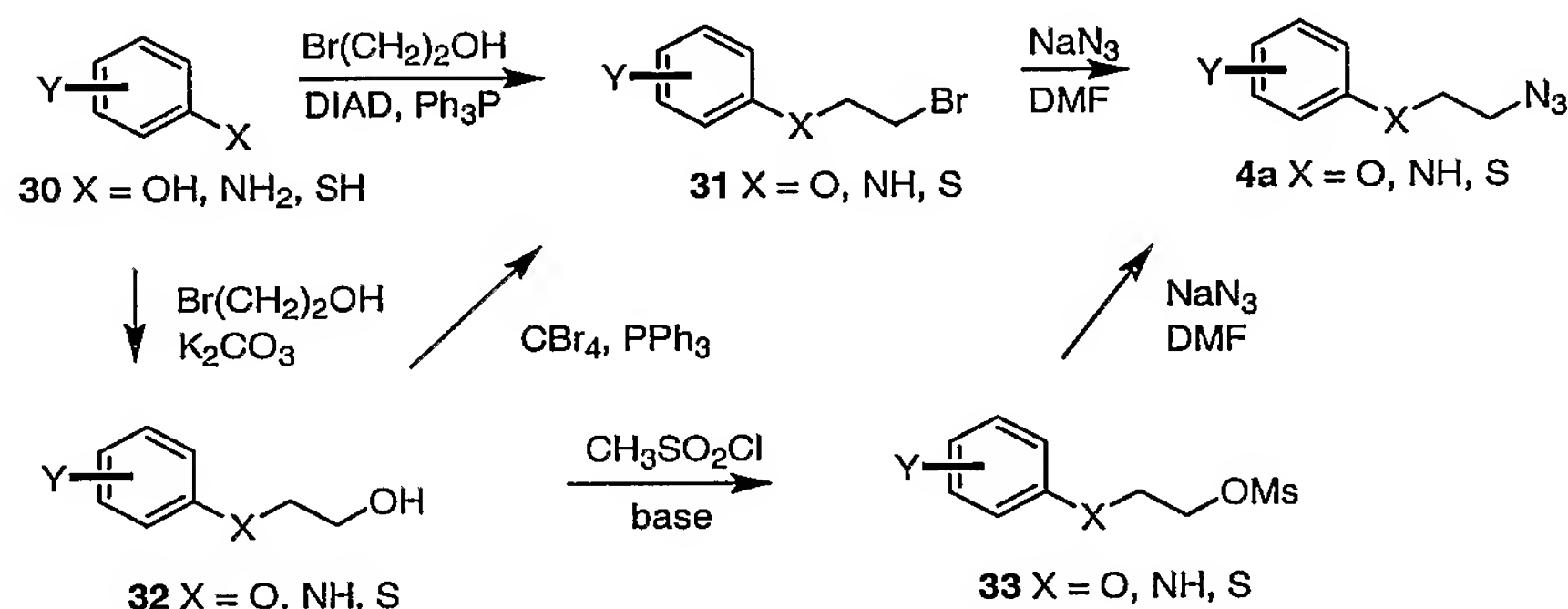


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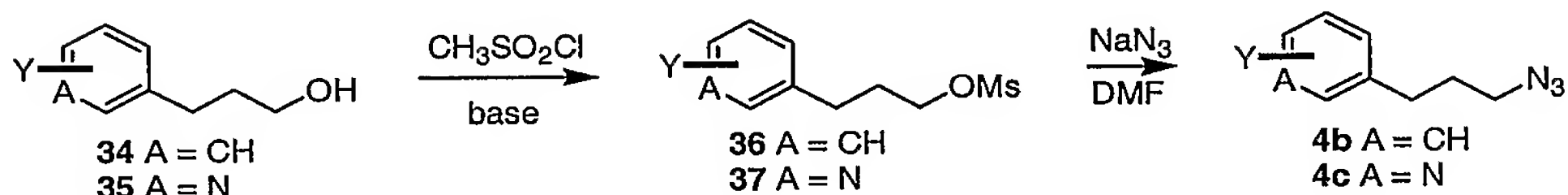
Intermediate azides of type **4** used to make compounds of the present invention can be synthesized using the methods exemplified in Schemes 7 and 8. Phenols, anilines, and thiophenols of type **30** can undergo Mitsunobu etherification processes with α,ω -halo alcohols (such as, but not limited to, 2-bromoethanol) to generate halides of type **31**. Displacement of the

20 halogen with sodium azide yields azides **4a**. Alternatively, direct alkylation of intermediates **30**
 with α,ω -halo alcohols yields alcohols of type **32**, which can be converted to halides **31** or
 converted to a sulfonate derivative such as **33**, for subsequent azide displacement to afford azides
4a. Arylpropanols of type **34**, and pyridylpropanols of type **35**, can be converted to azides **4b**
 and **4c** via sulfonates such as **36** and **37**. It will be appreciated that pyridyl derivatives with
 25 alternate substitution patterns (ortho and para), and alternate chain-lengths between the aryl
 moiety and the azide group can also be made using chemistry known in the art. It is intended
 that all such isomers and homologues are within the scope of the present invention.

Scheme 7

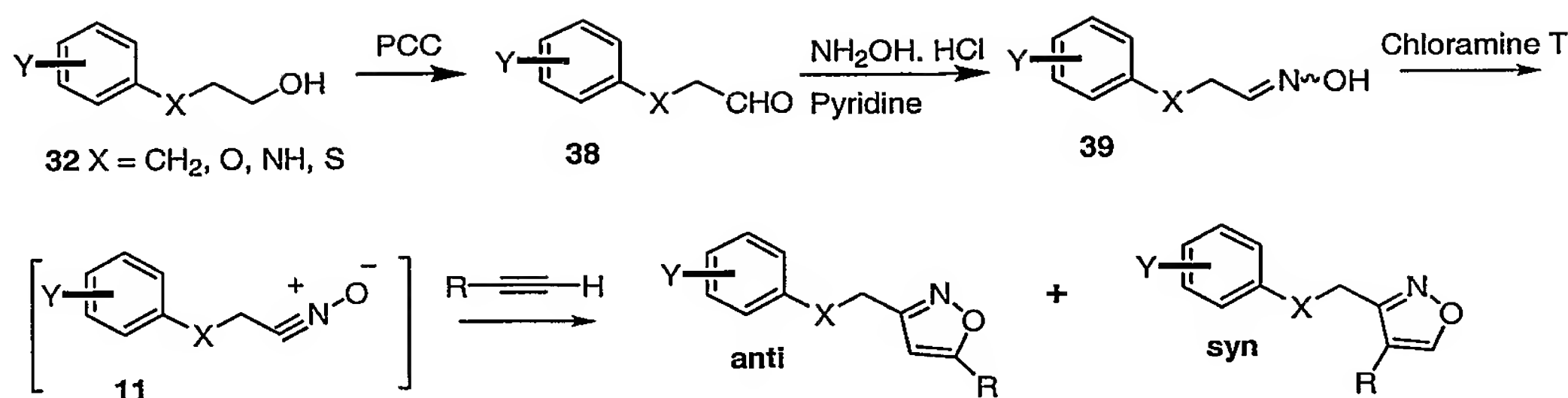


30 Scheme 8



Nitrile oxides of type **11** used to make compounds of the present invention can be
 synthesized using the method exemplified in Scheme 9. Substituted arylalkanols of type **32** (or
 35 pyridylalkanols) of various chain length between the aryl moiety and the alcohol group can be
 oxidized to aldehydes **38**. Conversion of the aldehyde to oximes **39** can be followed by
 conversion to intermediate nitrile oxides **11** using chloramine T (or other reagents used in
 combination with organic amine bases such as N-bromosuccinimide, N-chlorosuccinimide, t-
 butyl hypochlorite, lead tetraacetate etc.). The reaction to form the nitrile oxide can be run in the
 40 presence of an appropriate alkyne to trap the unstable intermediates **11** directly, affording a
 mixture of anti and syn isoxazole products.

20 Scheme 9



4. Characterization of Compounds of the Invention

25 Compounds designed, selected and/or optimized by methods described above, once produced, may be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules may be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

30 Furthermore, high-throughput screening may be used to speed up analysis using such assays. As a result, it may be possible to rapidly screen the molecules described herein for activity, for example, as anti-cancer, anti-bacterial, anti-fungal, anti-parasitic or anti-viral agents. Also, it may be possible to assay how the compounds interact with a ribosome or ribosomal subunit and/or are effective as modulators (for example, inhibitors) of protein synthesis using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin (1998) High Throughput Screening, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

40 (1) *Surface Binding Studies*. A variety of binding assays may be useful in screening new molecules for their binding activity. One approach includes surface plasmon resonance (SPR) that can be used to evaluate the binding properties of molecules of interest with respect to a ribosome, ribosomal subunit or a fragment thereof.

45 SPR methodologies measure the interaction between two or more macromolecules in real-time through the generation of a quantum-mechanical surface plasmon. One device, (BIAcore Biosensor RTM from Pharmacia Biosensor, Piscataway, N.J.) provides a focused beam of polychromatic light to the interface between a gold film (provided as a disposable biosensor "chip") and a buffer compartment that can be regulated by the user. A 100 nm thick "hydrogel"

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20 composed of carboxylated dextran that provides a matrix for the covalent immobilization of
analytes of interest is attached to the gold film. When the focused light interacts with the free
electron cloud of the gold film, plasmon resonance is enhanced. The resulting reflected light is
spectrally depleted in wavelengths that optimally evolved the resonance. By separating the
reflected polychromatic light into its component wavelengths (by means of a prism), and
25 determining the frequencies that are depleted, the BIAcore establishes an optical interface which
accurately reports the behavior of the generated surface plasmon resonance. When designed as
above, the plasmon resonance (and thus the depletion spectrum) is sensitive to mass in the
evanescent field (which corresponds roughly to the thickness of the hydrogel). If one component
of an interacting pair is immobilized to the hydrogel, and the interacting partner is provided
30 through the buffer compartment, the interaction between the two components can be measured in
real time based on the accumulation of mass in the evanescent field and its corresponding effects
of the plasmon resonance as measured by the depletion spectrum. This system permits rapid and
sensitive real-time measurement of the molecular interactions without the need to label either
component.

35 (2) *Fluorescence Polarization*. Fluorescence polarization (FP) is a measurement
technique that can readily be applied to protein-protein, protein-ligand, or RNA-ligand
interactions in order to derive IC_{50} s and K_d s of the association reaction between two molecules.
In this technique one of the molecules of interest is conjugated with a fluorophore. This is
generally the smaller molecule in the system (in this case, the compound of interest). The
40 sample mixture, containing both the ligand-probe conjugate and the ribosome, ribosomal subunit
or fragment thereof, is excited with vertically polarized light. Light is absorbed by the probe
fluorophores, and re-emitted a short time later. The degree of polarization of the emitted light is
measured. Polarization of the emitted light is dependent on several factors, but most importantly
on viscosity of the solution and on the apparent molecular weight of the fluorophore. With
45 proper controls, changes in the degree of polarization of the emitted light depends only on
changes in the apparent molecular weight of the fluorophore, which in-turn depends on whether
the probe-ligand conjugate is free in solution, or is bound to a receptor. Binding assays based on
FP have a number of important advantages, including the measurement of IC_{50} s and K_d s under
true homogenous equilibrium conditions, speed of analysis and amenity to automation, and
50 ability to screen in cloudy suspensions and colored solutions.

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20 (3) *Protein Synthesis*. It is contemplated that, in addition to characterization by the foregoing biochemical assays, the compound of interest may also be characterized as a modulator (for example, an inhibitor of protein synthesis) of the functional activity of the ribosome or ribosomal subunit.

Furthermore, more specific protein synthesis inhibition assays may be performed by
25 administering the compound to a whole organism, tissue, organ, organelle, cell, a cellular or subcellular extract, or a purified ribosome preparation and observing its pharmacological and inhibitory properties by determining, for example, its inhibition constant (IC_{50}) for inhibiting protein synthesis. Incorporation of 3H leucine or ^{35}S methionine, or similar experiments can be performed to investigate protein synthesis activity. A change in the amount or the rate of protein
30 synthesis in the cell in the presence of a molecule of interest indicates that the molecule is a modulator of protein synthesis. A decrease in the rate or the amount of protein synthesis indicates that the molecule is a inhibitor of protein synthesis.

Furthermore, the compounds may be assayed for anti-proliferative or anti-infective properties on a cellular level. For example, where the target organism is a microorganism, the
35 activity of compounds of interest may be assayed by growing the microorganisms of interest in media either containing or lacking the compound. Growth inhibition may be indicative that the molecule may be acting as a protein synthesis inhibitor. More specifically, the activity of the compounds of interest against bacterial pathogens may be demonstrated by the ability of the compound to inhibit growth of defined strains of human pathogens. For this purpose, a panel of
40 bacterial strains can be assembled to include a variety of target pathogenic species, some containing resistance mechanisms that have been characterized. Use of such a panel of organisms permits the determination of structure-activity relationships not only in regards to potency and spectrum, but also with a view to obviating resistance mechanisms. The assays may be performed in microtiter trays according to conventional methodologies as published by The
45 National Committee for Clinical Laboratory Standards (NCCLS) guidelines (NCCLS. M7-A5- Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Fifth Edition. NCCLS Document M100-S12/M7 (ISBN 1-56238-394-9)).

5. Formulation and Administration

The compounds of the invention may be useful in the prevention or treatment of a variety
50 of human or other animal, including mammalian and non mammalian, disorders, including for

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20 example, bacterial infection, fungal infections, viral infections, parasitic diseases, and cancer. It
is contemplated that, once identified, the active molecules of the invention may be incorporated
into any suitable carrier prior to use. The dose of active molecule, mode of administration and
use of suitable carrier will depend upon the intended recipient and target organism. The
formulations, both for veterinary and for human medical use, of compounds according to the
25 present invention typically include such compounds in association with a pharmaceutically
acceptable carrier.

The carrier(s) should be "acceptable" in the sense of being compatible with the other
ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable
carriers, in this regard, are intended to include any and all solvents, dispersion media, coatings,
30 anti-bacterial and anti-fungal agents, isotonic and absorption delaying agents, and the like,
compatible with pharmaceutical administration. The use of such media and agents for
pharmaceutically active substances is known in the art. Except insofar as any conventional
media or agent is incompatible with the active compound, use thereof in the compositions is
contemplated. Supplementary active compounds (identified or designed according to the
35 invention and/or known in the art) also can be incorporated into the compositions. The
formulations may conveniently be presented in dosage unit form and may be prepared by any of
the methods well known in the art of pharmacy/microbiology. In general, some formulations are
prepared by bringing the compound into association with a liquid carrier or a finely divided solid
carrier or both, and then, if necessary, shaping the product into the desired formulation.

40 A pharmaceutical composition of the invention should be formulated to be compatible
with its intended route of administration. Examples of routes of administration include oral or
parenteral, for example, intravenous, intradermal, inhalation, transdermal (topical), transmucosal,
and rectal administration. Solutions or suspensions used for parenteral, intradermal, or
subcutaneous application can include the following components: a sterile diluent such as water
45 for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or
other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens;
antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as
ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for
the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or
50 bases, such as hydrochloric acid or sodium hydroxide.

20 Useful solutions for oral or parenteral administration can be prepared by any of the methods well known in the pharmaceutical art, described, for example, in Remington's Pharmaceutical Sciences, (Gennaro, A., ed.), Mack Pub., (1990). Formulations for parenteral administration can also include glycocholate for buccal administration, methoxysalicylate for rectal administration, or citric acid for vaginal administration. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. 25 Suppositories for rectal administration also can be prepared by mixing the drug with a non-irritating excipient such as cocoa butter, other glycerides, or other compositions which are solid at room temperature and liquid at body temperatures. Formulations also can include, for example, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, and 30 hydrogenated naphthalenes. Formulations for direct administration can include glycerol and other compositions of high viscosity. Other potentially useful parenteral carriers for these drugs include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration can contain as excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9- 35 lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Retention enemas also can be used for rectal delivery.

Formulations of the present invention suitable for oral administration may be in the form of: discrete units such as capsules, gelatin capsules, sachets, tablets, troches, or lozenges, each 40 containing a predetermined amount of the drug; a powder or granular composition; a solution or a suspension in an aqueous liquid or non-aqueous liquid; or an oil-in-water emulsion or a water-in-oil emulsion. The drug may also be administered in the form of a bolus, electuary or paste. A tablet may be made by compressing or moulding the drug optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the 45 drug in a free-flowing form such as a powder or granules, optionally mixed by a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered drug and suitable carrier moistened with an inert liquid diluent.

Oral compositions generally include an inert diluent or an edible carrier. For the purpose 50 of oral therapeutic administration, the active compound can be incorporated with excipients. Oral compositions prepared using a fluid carrier for use as a mouthwash include the compound

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20 in the fluid carrier and are applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent
25 such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of
30 sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example,
35 water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the
40 composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated
45 above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze-drying which yields a powder of the active ingredient plus any
50 additional desired ingredient from a previously sterile-filtered solution thereof.

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20 Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the drug that may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the drug for both intra-articular and ophthalmic administration.

25 Formulations suitable for topical administration, including eye treatment, include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. Formulations for topical administration to the skin surface can be prepared by dispersing the drug with a dermatologically acceptable carrier such as a lotion, cream, ointment or soap.

30 Particularly useful are carriers capable of forming a film or layer over the skin to localize application and inhibit removal. For topical administration to internal tissue surfaces, the agent can be dispersed in a liquid tissue adhesive or other substance known to enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or fibrinogen/thrombin solutions can be used to advantage. Alternatively, tissue-coating solutions, such as pectin-containing
35 formulations can be used.

 For inhalation treatments, inhalation of powder (self-propelling or spray formulations) dispensed with a spray can, a nebulizer, or an atomizer can be used. Such formulations can be in the form of a fine powder for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing formulations. In the case of self-propelling solution and spray
40 formulations, the effect may be achieved either by choice of a valve having the desired spray characteristics (*i.e.*, being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder in controlled particle size. For administration by inhalation, the compounds also can be delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such
45 as carbon dioxide, or a nebulizer.

 Systemic administration also can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants generally are known in the art, and include, for example, for transmucosal administration, detergents and bile salts. Transmucosal
50 administration can be accomplished through the use of nasal sprays or suppositories. For

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20 transdermal administration, the active compounds typically are formulated into ointments, salves, gels, or creams as generally known in the art.

The active compounds may be prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can
25 be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

30 Oral or parenteral compositions can be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the
35 invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals. Furthermore, administration can be by periodic injections of a bolus, or can be made more continuous by intravenous, intramuscular or intraperitoneal administration from an external reservoir (*e.g.*, an
40 intravenous bag).

Where adhesion to a tissue surface is desired the composition can include the drug dispersed in a fibrinogen-thrombin composition or other bioadhesive. The compound then can be painted, sprayed or otherwise applied to the desired tissue surface. Alternatively, the drugs can be formulated for parenteral or oral administration to humans or other mammals, for
45 example, in therapeutically effective amounts, *e.g.*, amounts that provide appropriate concentrations of the drug to target tissue for a time sufficient to induce the desired effect.

Where the active compound is to be used as part of a transplant procedure, it can be provided to the living tissue or organ to be transplanted prior to removal of tissue or organ from the donor. The compound can be provided to the donor host. Alternatively or, in addition, once
50 removed from the donor, the organ or living tissue can be placed in a preservation solution containing the active compound. In all cases, the active compound can be administered directly

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20 to the desired tissue, as by injection to the tissue, or it can be provided systemically, either by oral or parenteral administration, using any of the methods and formulations described herein and/or known in the art. Where the drug comprises part of a tissue or organ preservation solution, any commercially available preservation solution can be used to advantage. For example, useful solutions known in the art include Collins solution, Wisconsin solution, Belzer
25 solution, Eurocollins solution and lactated Ringer's solution.

The compounds of the present invention can be administered directly to a tissue locus by applying the compound to a medical device that is placed in contact with the tissue. An example of a medical device is a stent, which contains or is coated with one or more of the compounds of the present invention.

30 For example, an active compound may be applied to a stent at the site of vascular injury. Stents can be prepared by any of the methods well known in the pharmaceutical art. See, e.g., Fattori, R. and Piva, T., "Drug Eluting Stents in Vascular Intervention," Lancet, 2003, 361, 247-249; Morice, M. C., "A New Era in the Treatment of Coronary Disease?" European Heart Journal, 2003, 24, 209-211; and Toutouzas, K. et al., "Sirolimus-Eluting Stents: A Review of
35 Experimental and Clinical Findings," Z. Kardiol., 2002, 91(3), 49-57. The stent may be fabricated from stainless steel or another bio-compatible metal, or it may be made of a bio-compatible polymer. The active compound may be linked to the stent surface, embedded and released from polymer materials coated on the stent, or surrounded by and released through a carrier which coats or spans the stent. The stent may be used to administer single or multiple
40 active compounds to tissues adjacent to the stent.

Active compound as identified or designed by the methods described herein can be administered to individuals to treat disorders (prophylactically or therapeutically). In conjunction with such treatment, pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) may be
45 considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a drug as well as tailoring the dosage and/or therapeutic regimen of treatment with the drug.

50 In therapeutic use for treating, or combating, bacterial infections in mammals, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally

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20 and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level or tissue level of active component in the animal undergoing treatment which will be anti-microbially effective. Generally, an effective amount of dosage of active component will be in the range of from about 0.1 to about 100, more preferably from about 1.0 to about 50 mg/kg of body weight/day. The amount administered will also likely depend on such variables as the type
25 and extent of disease or indication to be treated, the overall health status of the particular patient, the relative biological efficacy of the compound delivered, the formulation of the drug, the presence and types of excipients in the formulation, and the route of administration. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage may
30 be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, for example, two to four times per day.

Various disease states or conditions in humans and other mammals are found to be caused by or mediated by nonsense or missense mutations. These mutations cause or mediate
35 the disease state or condition by adversely affecting, for example, protein synthesis, folding, trafficking and/or function. Examples of disease states or conditions in which an appreciable percentage of the disease or condition is believed to result from nonsense or missense mutations include hemophilia (factor VIII gene), neurofibromatosis (NF1 and NF2 genes), retinitis pigmentosa (human USH2A gene), bullous skin diseases like Epidermolysis bullosa pruriginosa
40 (COL7A1 gene), cystic fibrosis (cystic fibrosis transmembrane regulator gene), breast and ovarian cancer (BRCA1 and BRCA2 genes), Duchenne muscular dystrophy (dystrophin gene), colon cancer (mismatch repair genes, predominantly in MLH1 and MSH2), and lysosomal storage disorders such as Neimann-Pick disease (acid sphingomyelinase gene). See Sanders CR, Myers JK. Disease-related misassembly of membrane proteins. Annu Rev Biophys Biomol
45 Struct. 2004;33:25-51; National Center for Biotechnology Information (U.S.) Genes and disease Bethesda, MD : NCBI, NLM ID: 101138560 [Book]; and Raskó, István; Downes, C S Genes in medicine : molecular biology and human genetic disorders 1st ed. London ; New York : Chapman & Hall, 1995. NLM ID: 9502404 [Book]. The compounds of the present invention can be used to treat or prevent a disease state in a mammal caused or mediated by such nonsense
50 or missense mutations by administering to a mammal in need thereof an effective amount of the present invention to suppress the nonsense or missense mutation involved in the disease state.

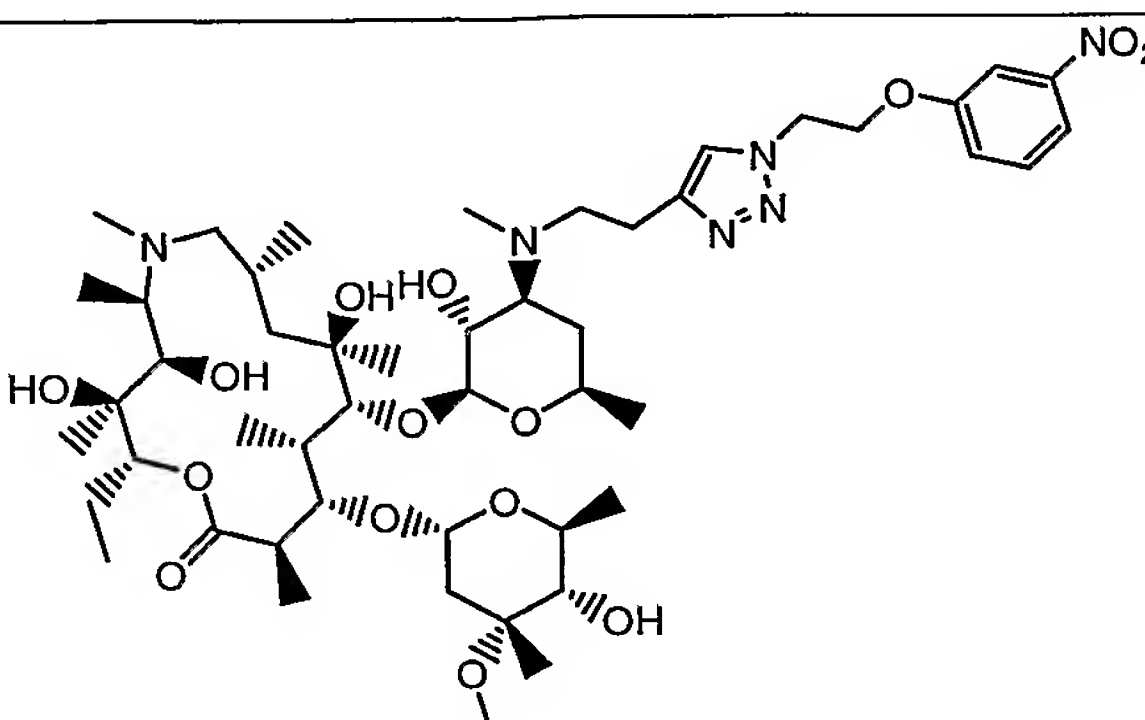
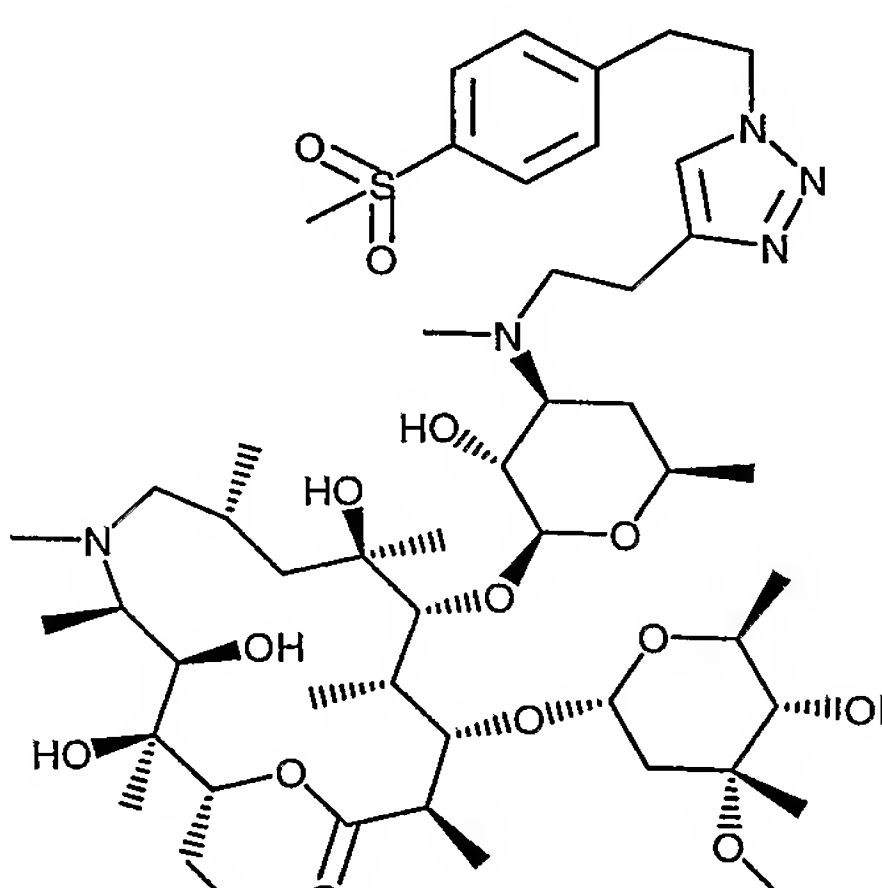
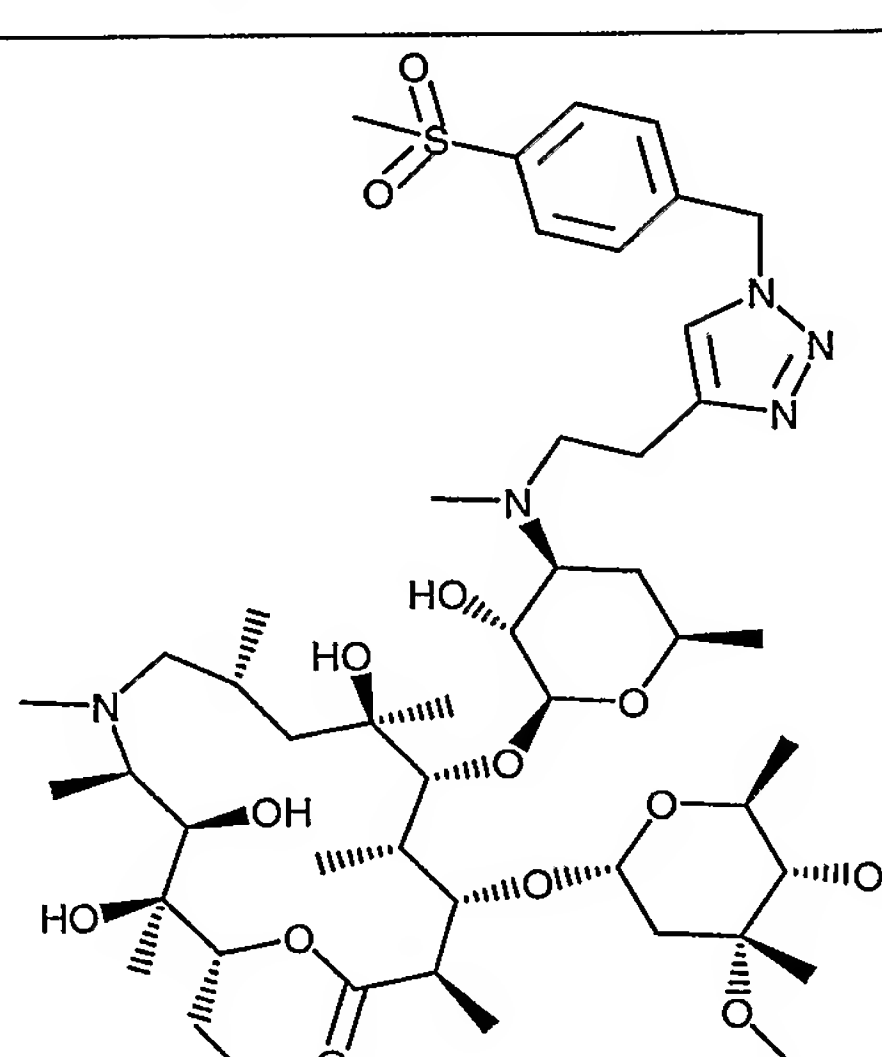
20 **6. Examples**

 Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance 300 or Avance 500 spectrometer, or in some cases a GE-Nicolet 300 spectrometer. Common reaction solvents were either high performance liquid chromatography (HPLC) grade or American Chemical Society (ACS) grade, and anhydrous as obtained from the manufacturer unless
25 otherwise noted. "Chromatography" or "purified by silica gel" refers to flash column chromatography using silica gel (EM Merck, Silica Gel 60, 230-400 mesh) unless otherwise noted.

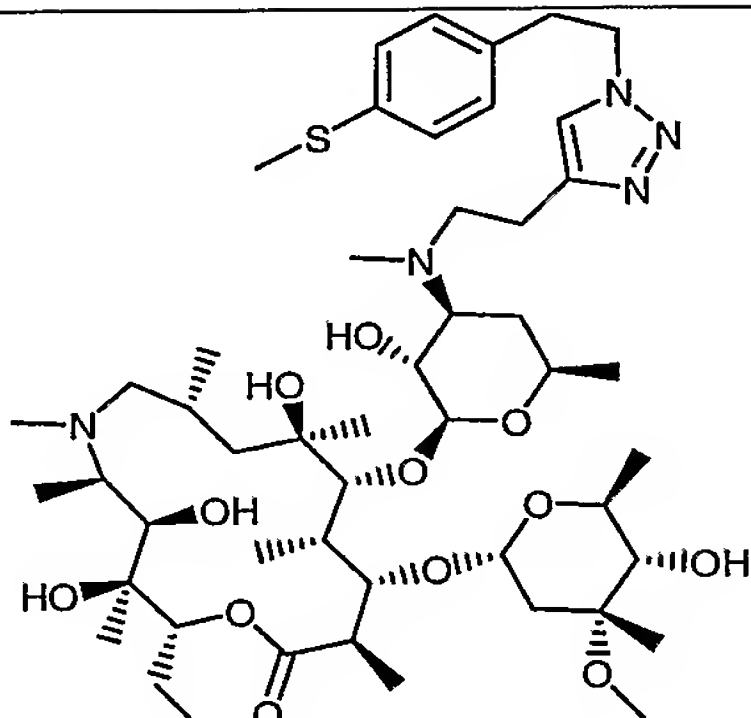
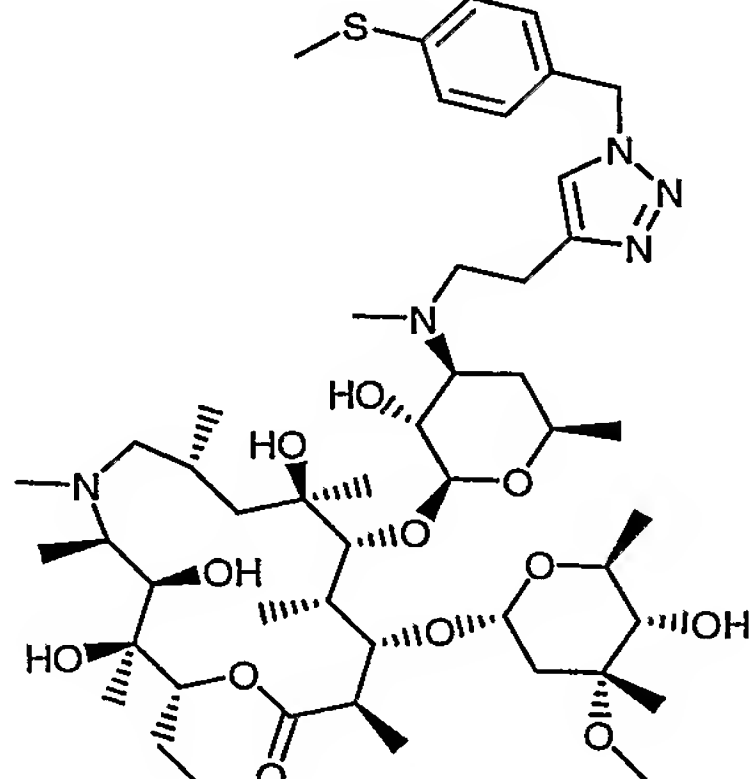
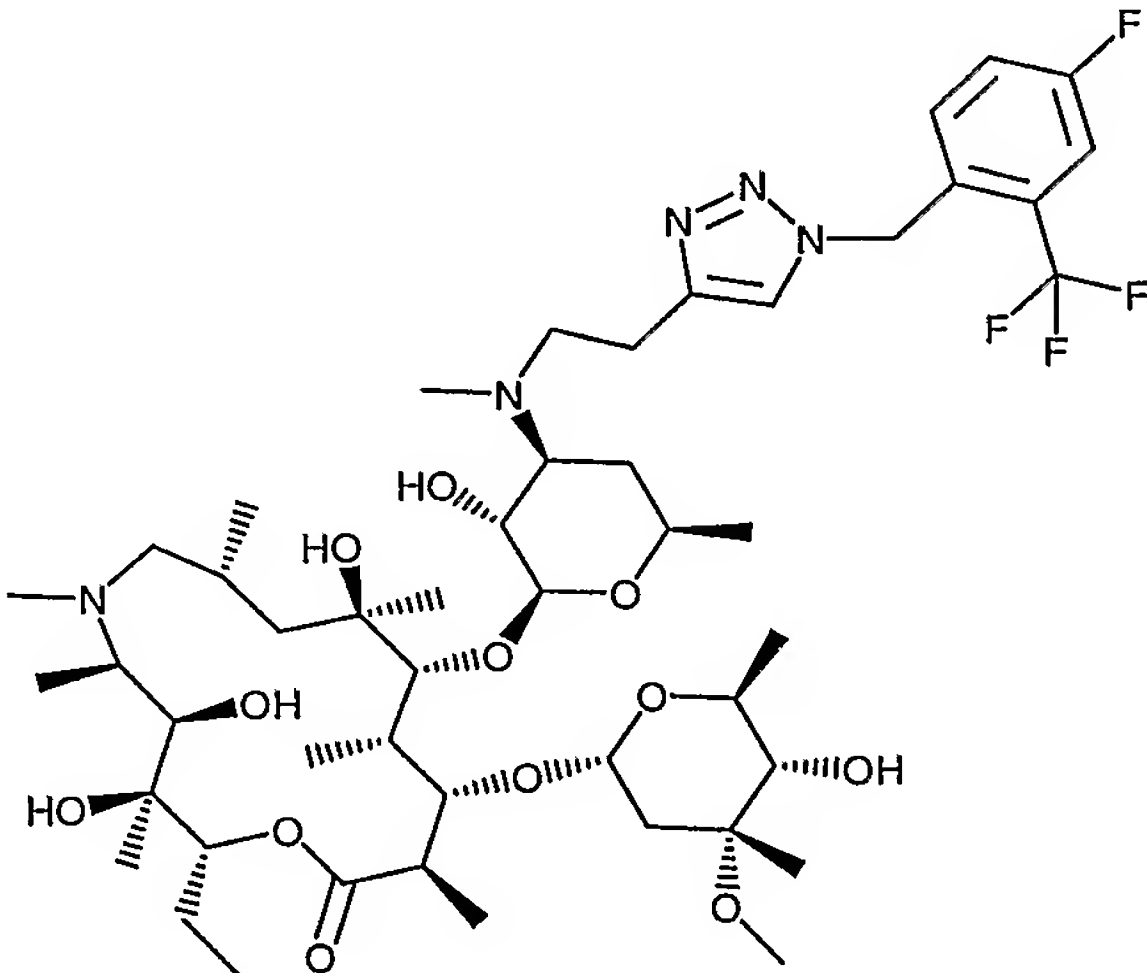
 The compound numbers, e.g., **1**, **2**, **3**, etc. used in this section 6 of the present application and entitled "**6. Examples**", are for reference within this section 6 only and do not refer to and
30 are not to be confused with any similarly numbered compounds in section 3 of the present application and entitled "**3. Synthesis of the Compounds of the Invention**".

 Compounds synthesized in accordance with the invention are listed in Table 1.

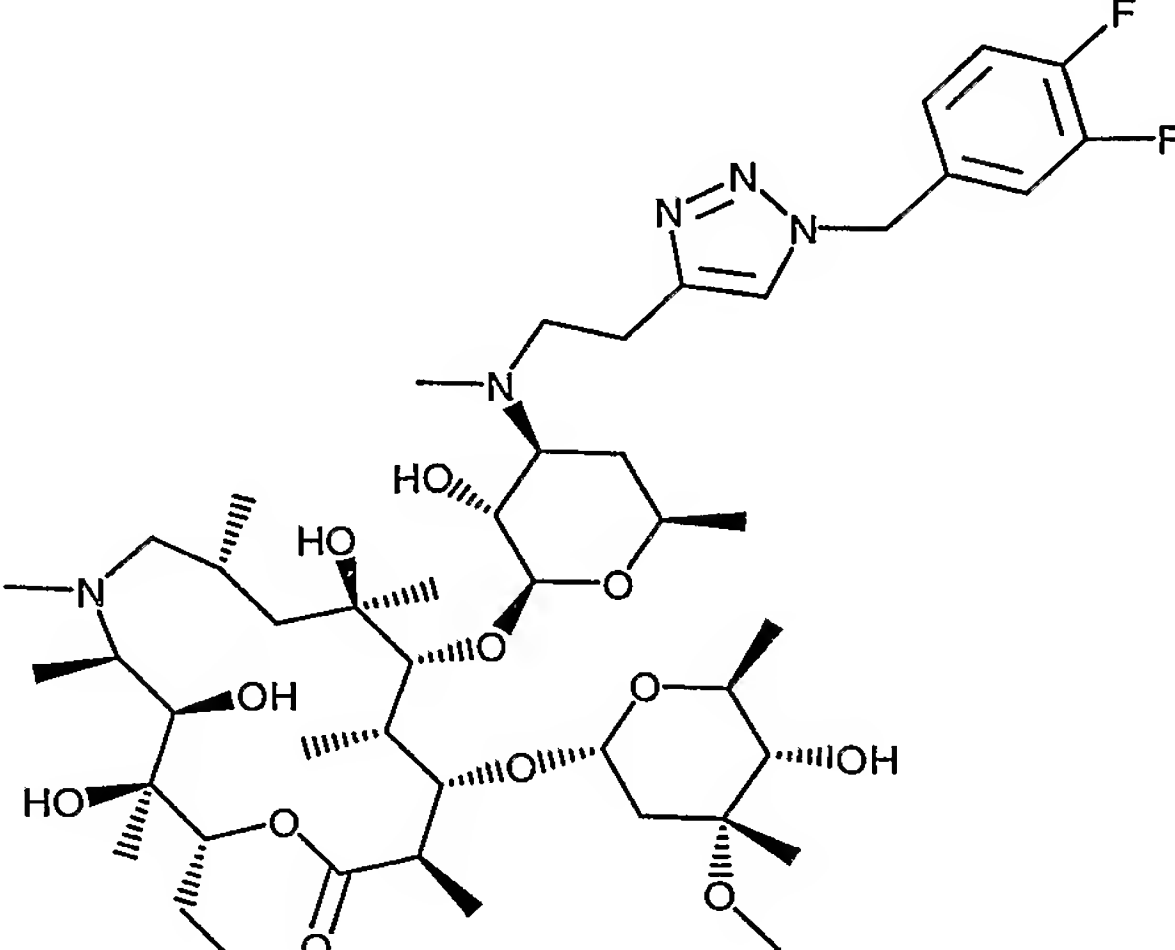
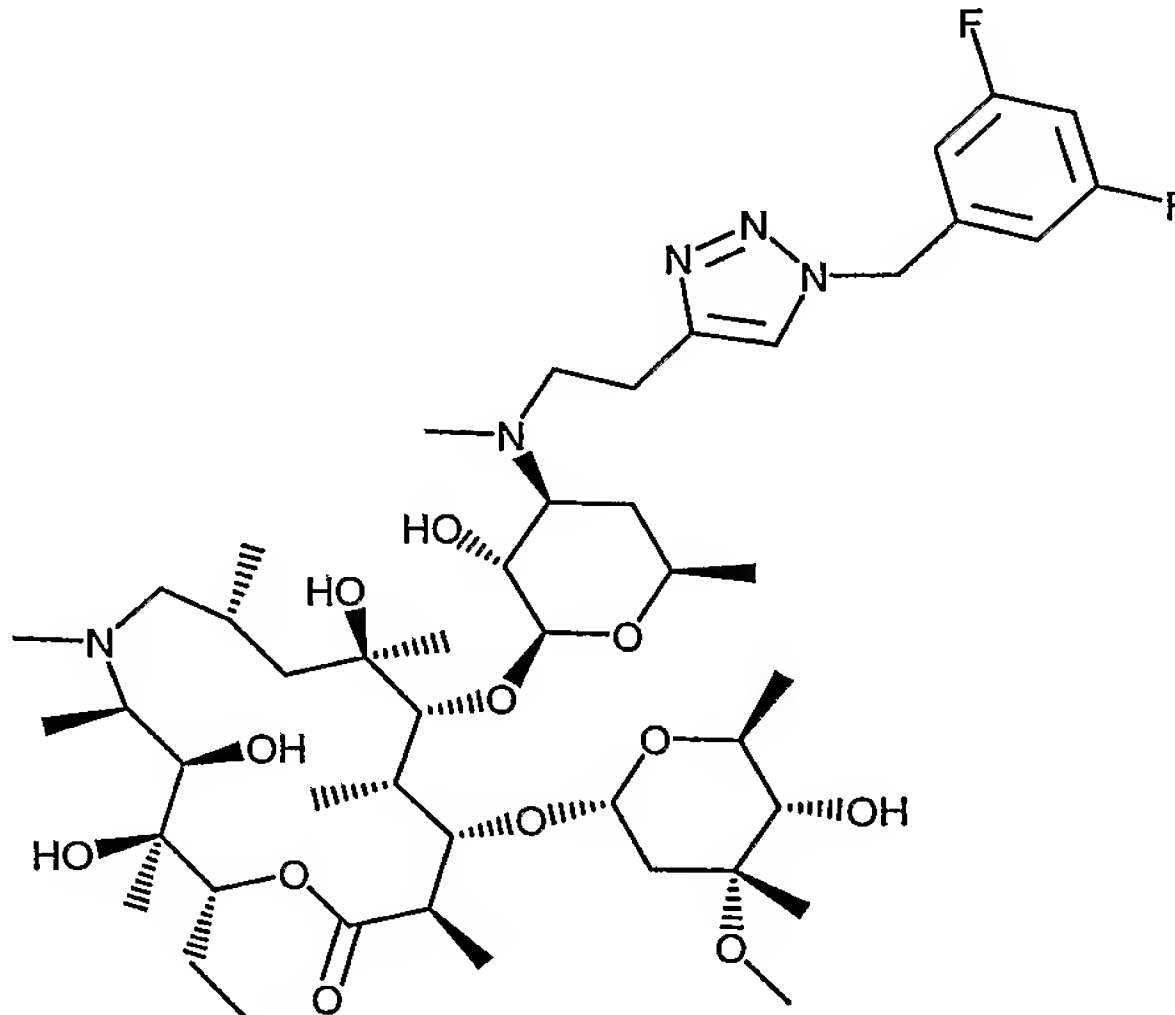
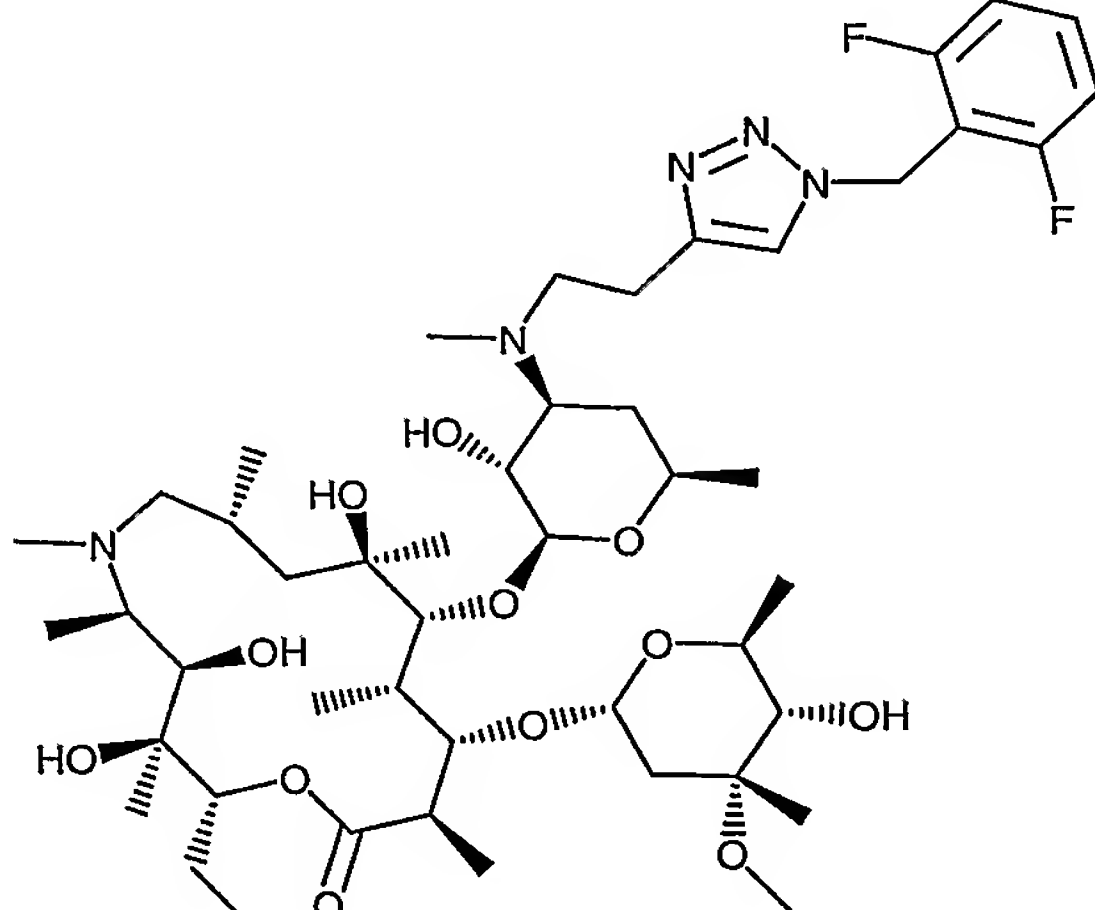
Table 1

Compound Number	Structure
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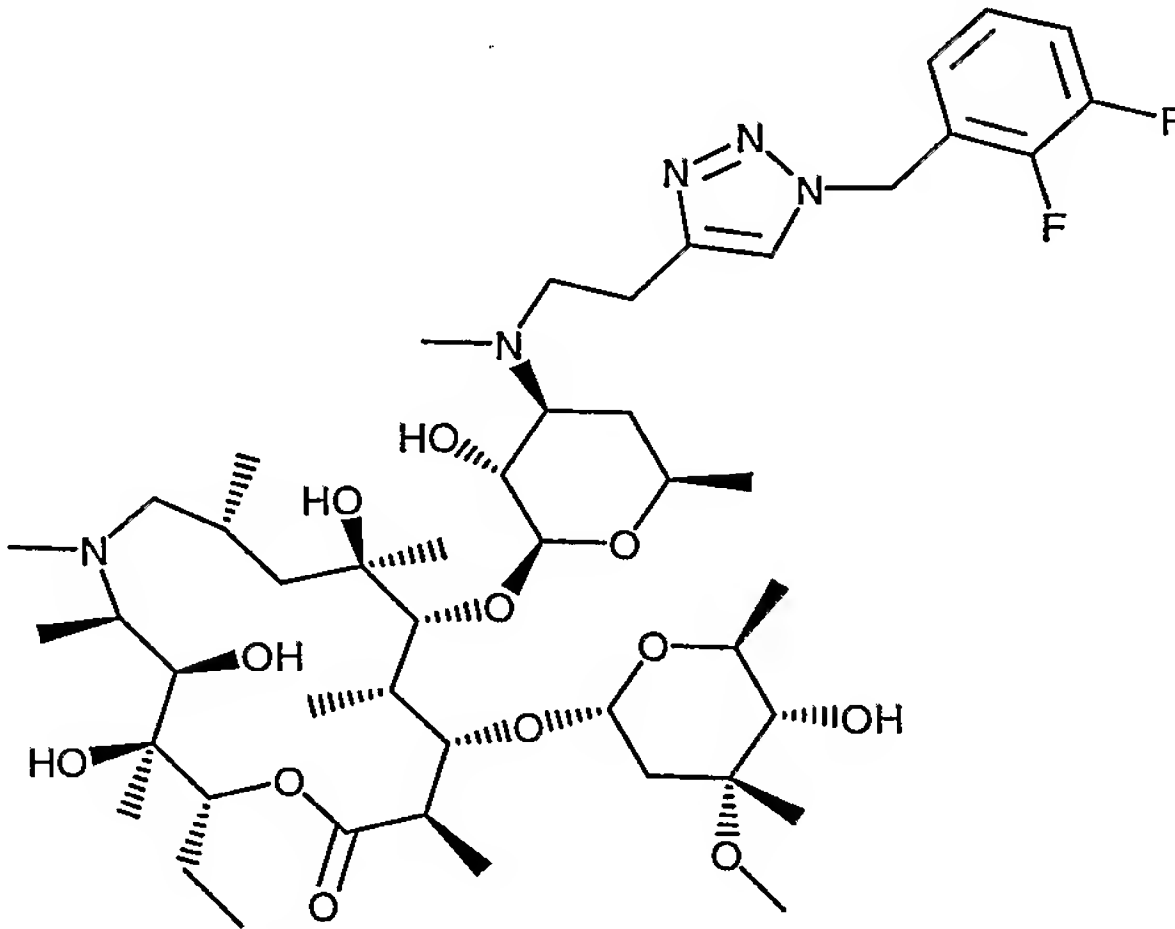
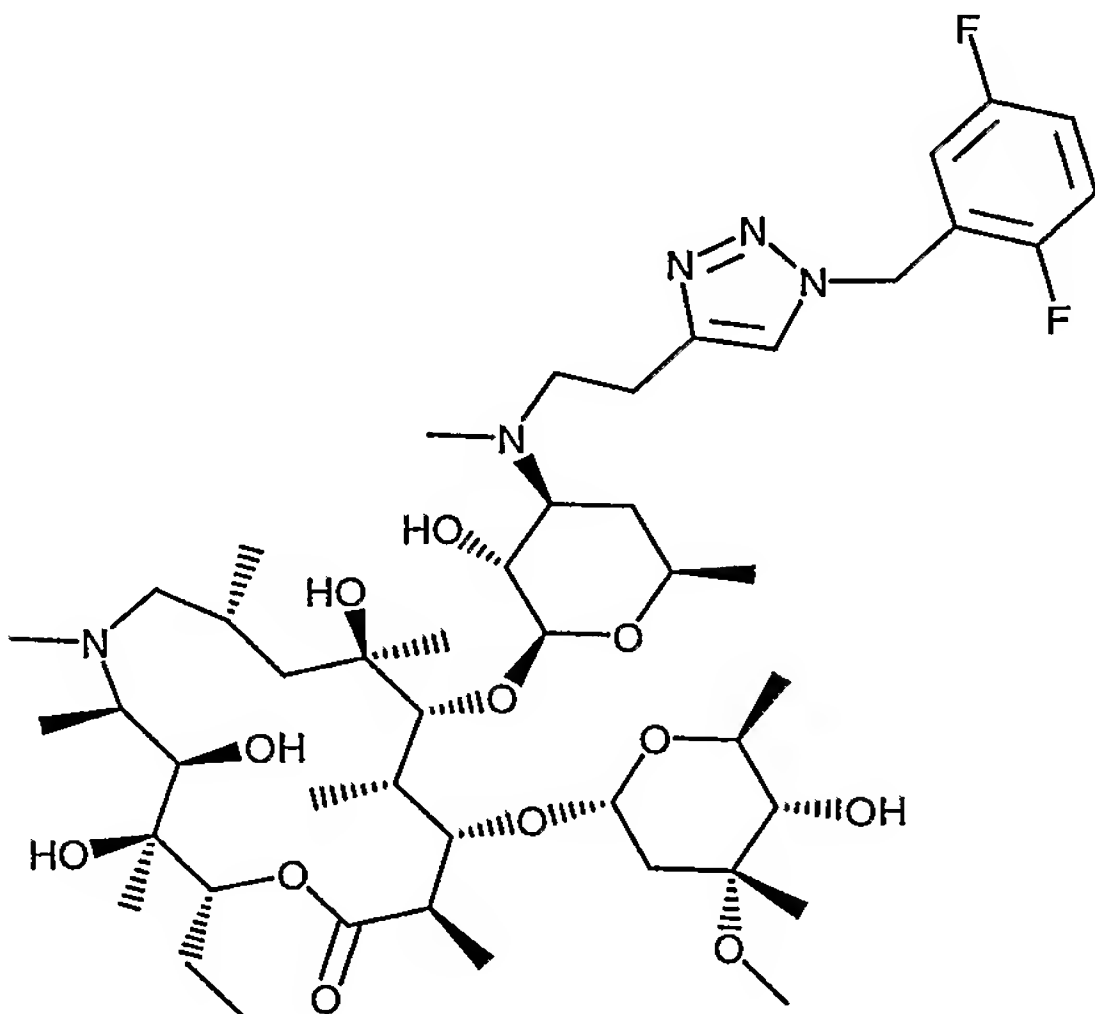
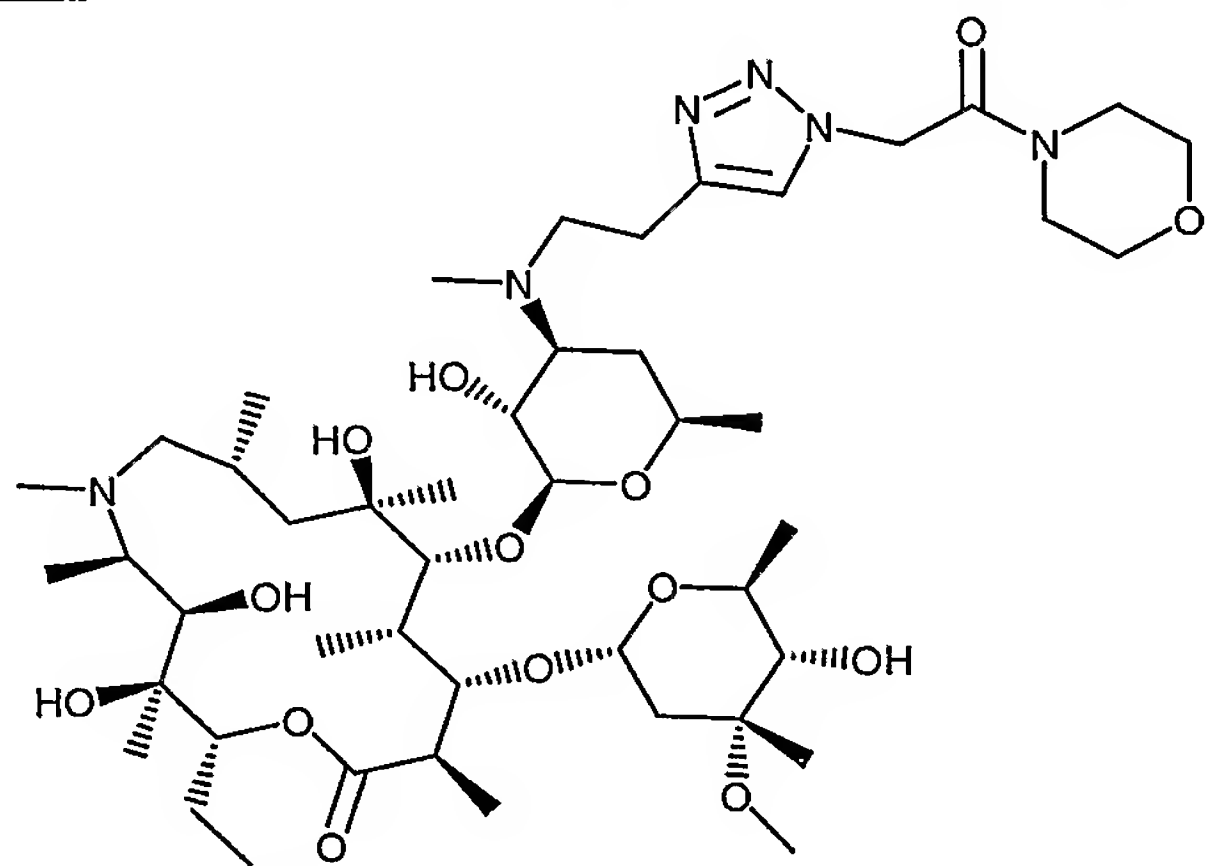
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104	
105	
106	

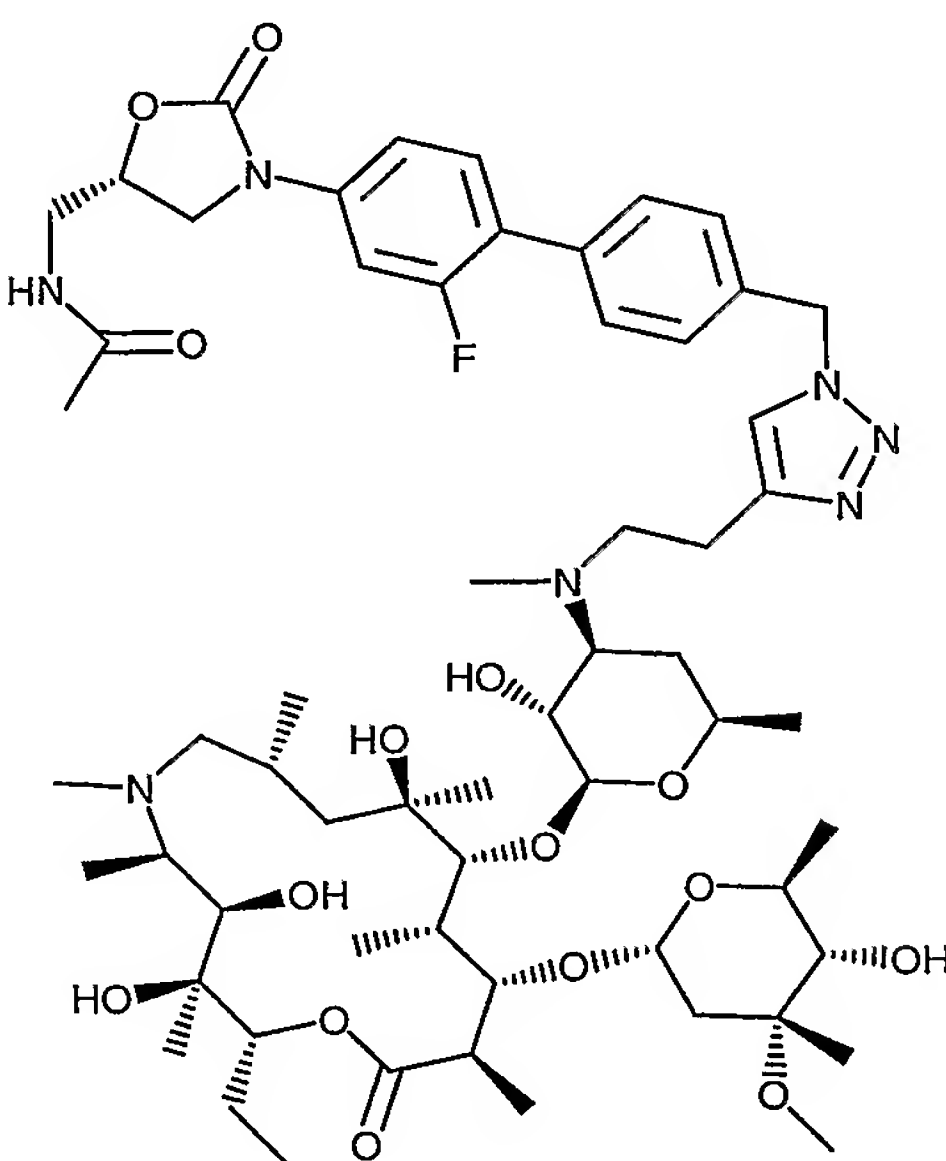
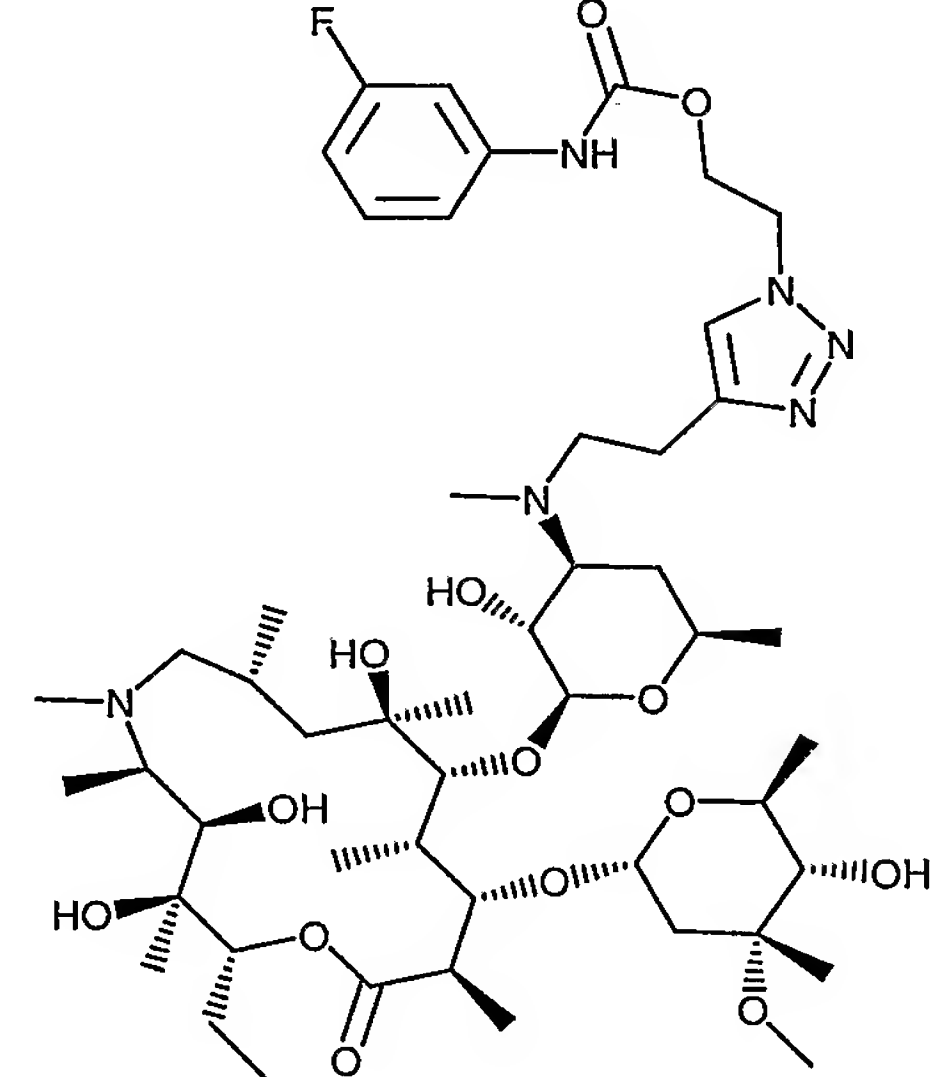
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107	
108	
109	

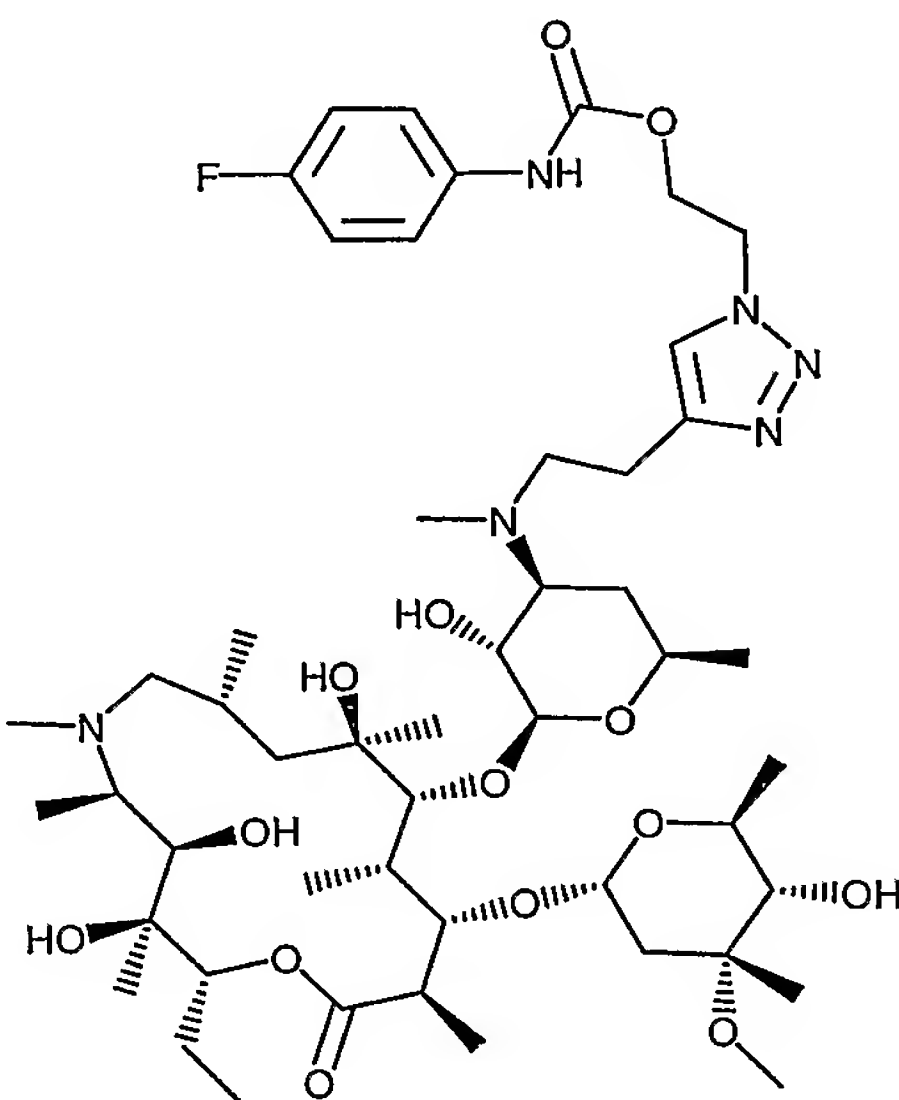
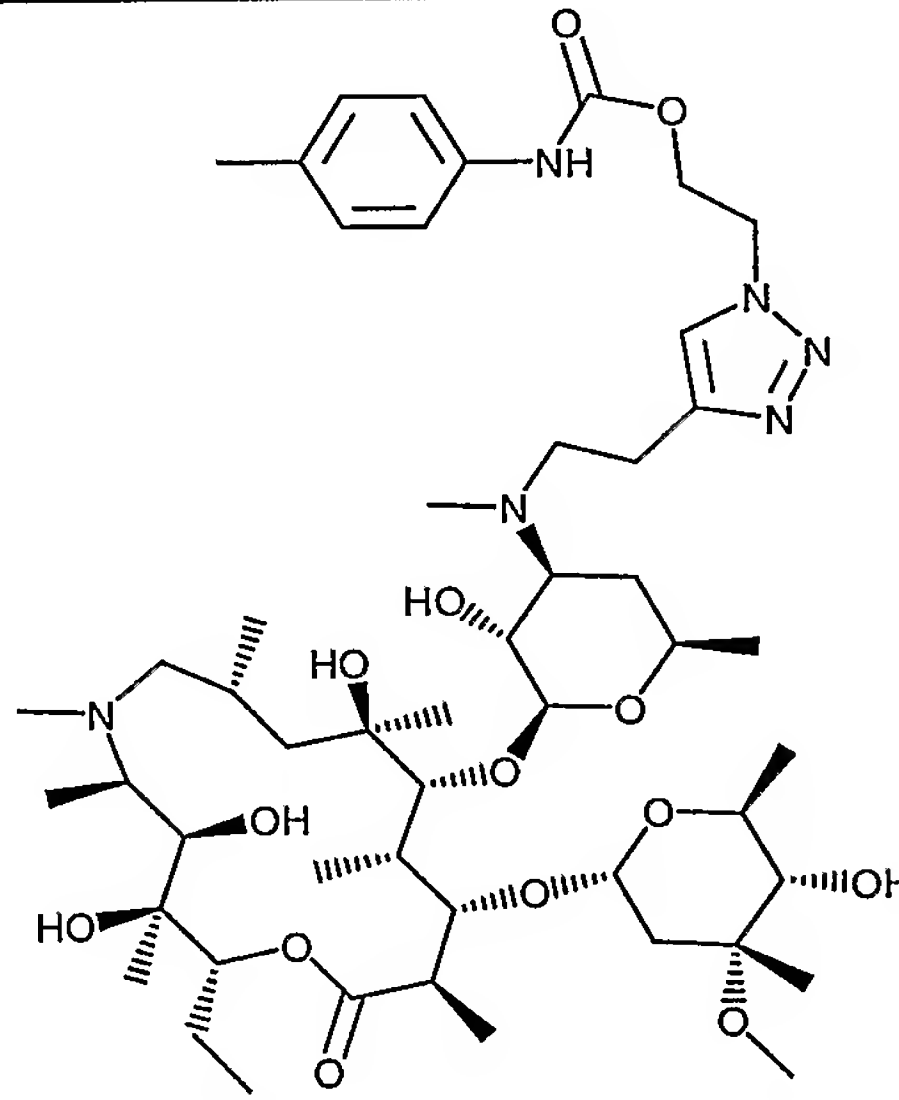
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110	
111	
112	

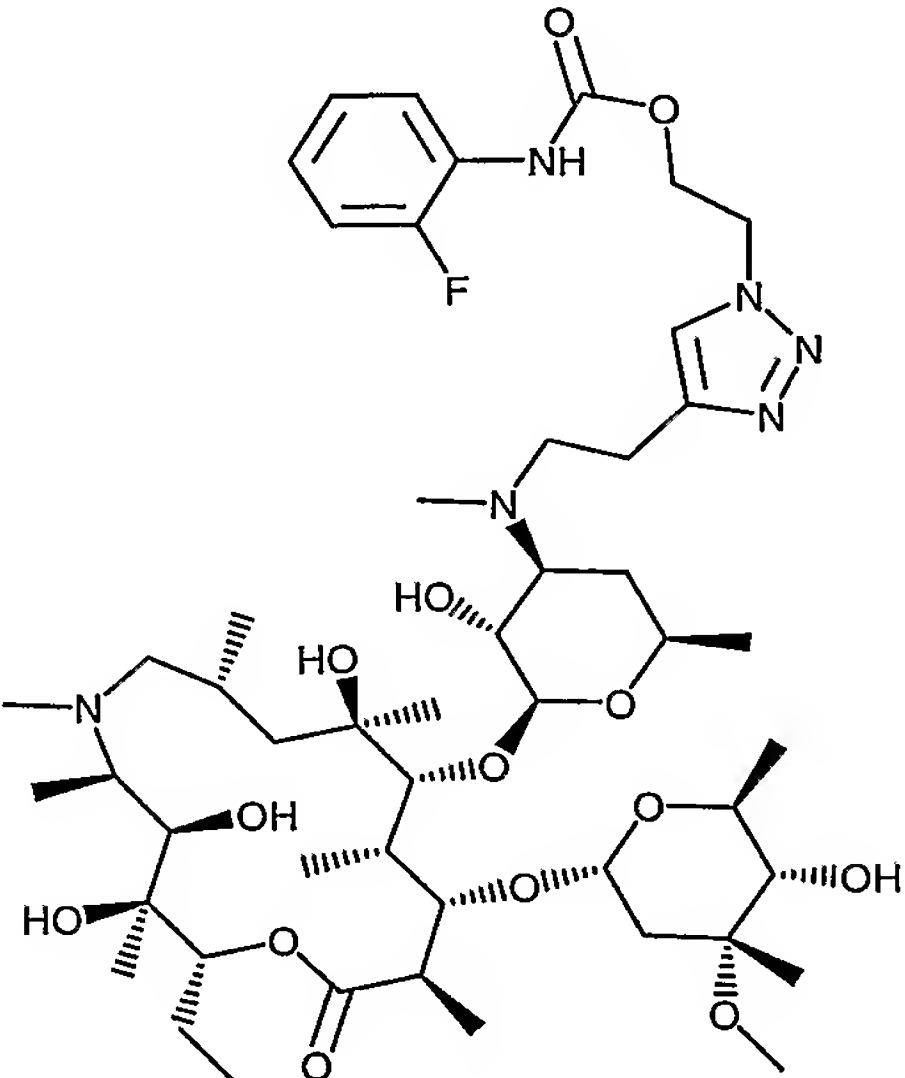
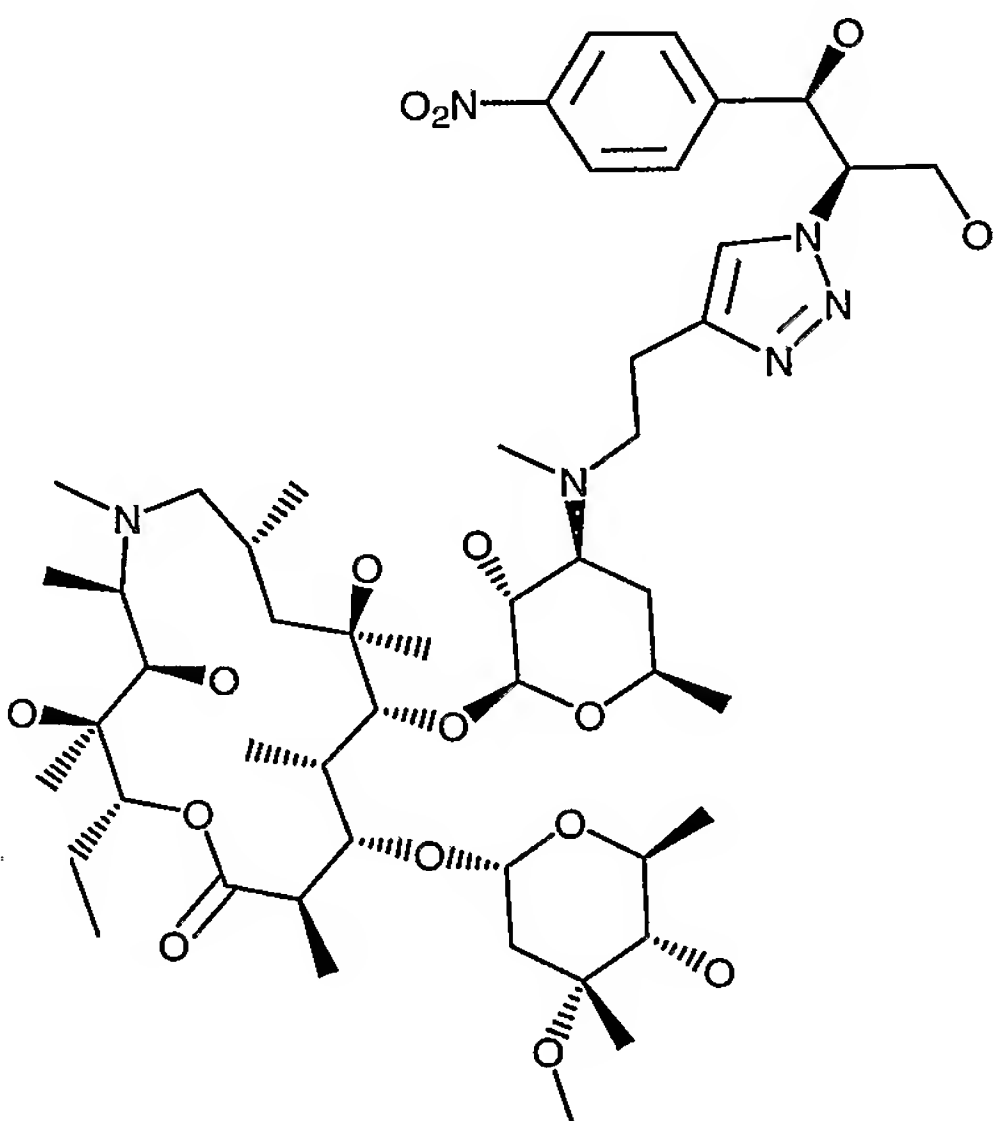
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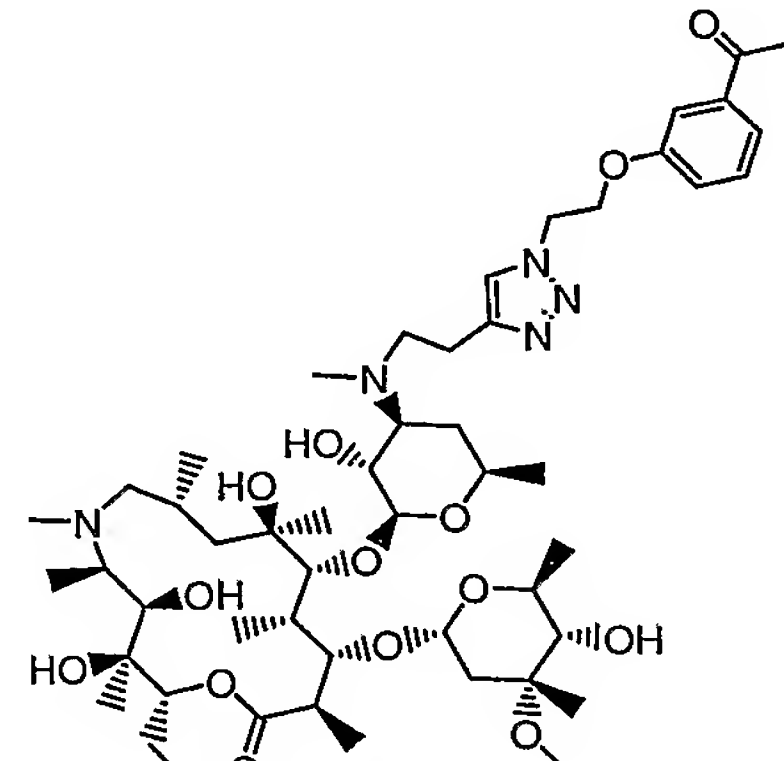
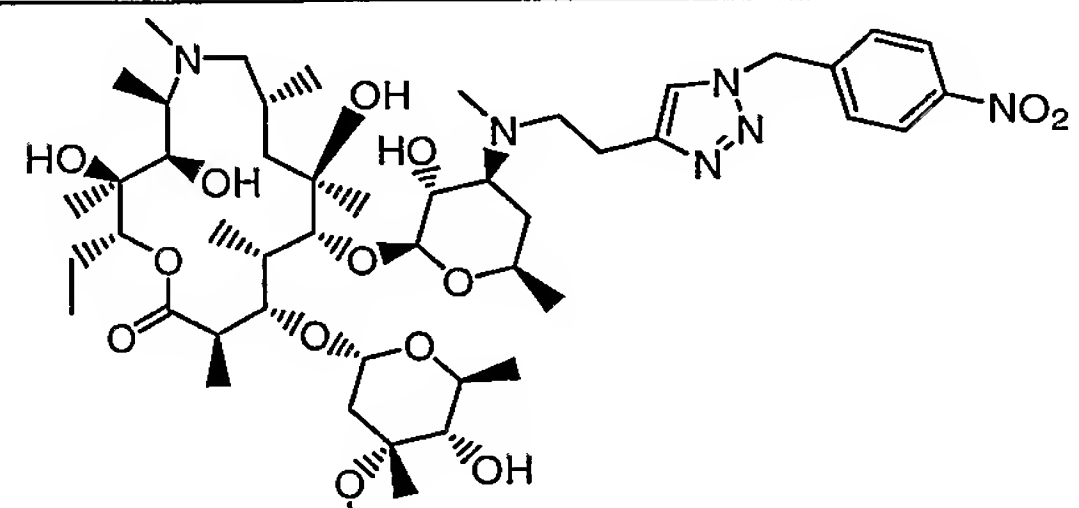
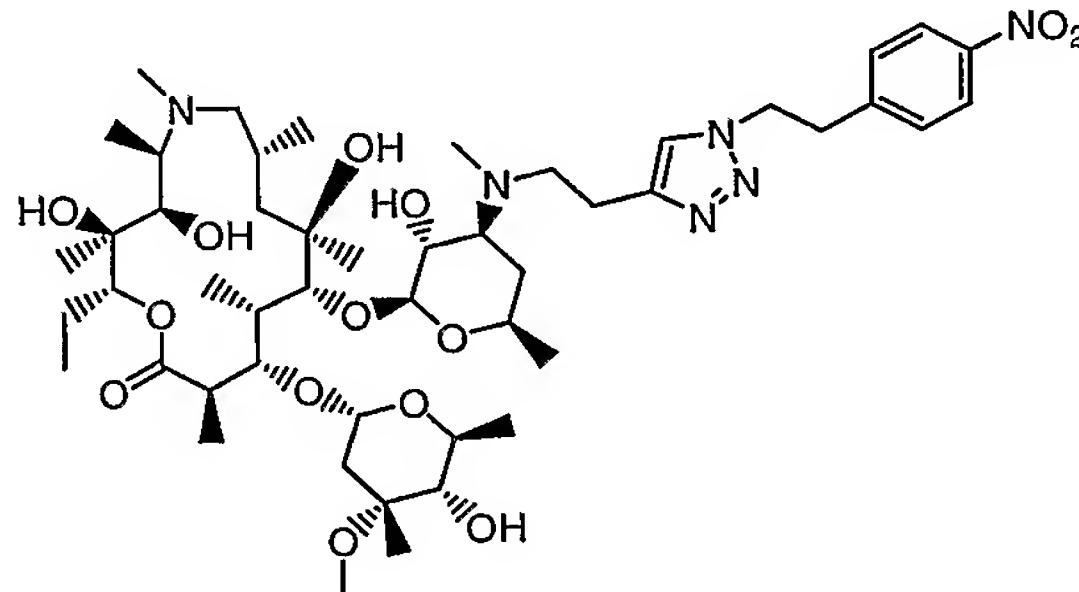
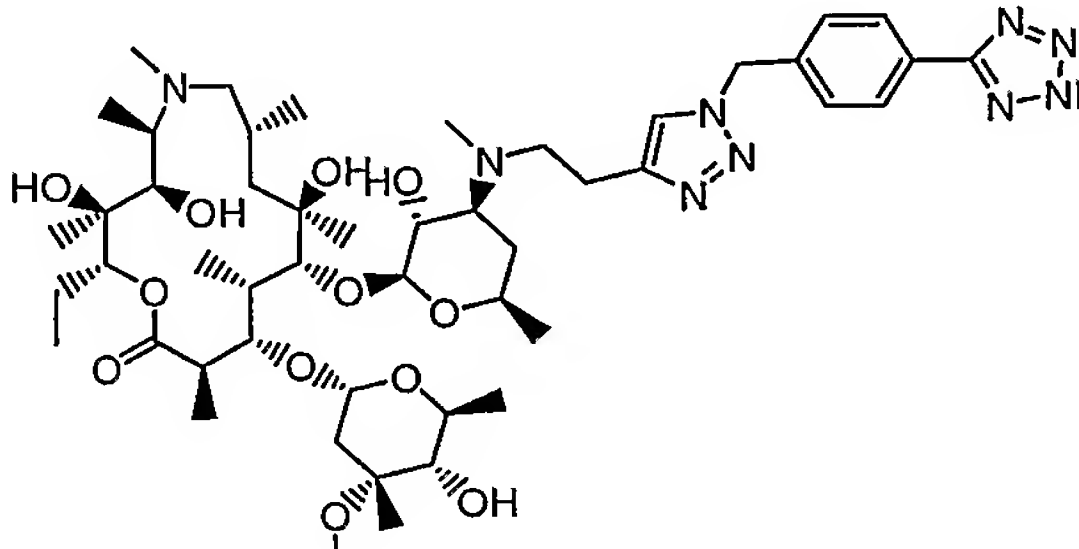
113	 <p>Chemical structure 113 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a carbonyl group. The core is substituted with a 4-fluorophenyl group, a 4-(1H-tetrazol-1-yl)phenyl group, and a 4-(2-oxo-2-(prop-1-en-1-yl)oxy)phenyl group.</p>
114	 <p>Chemical structure 114 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a carbonyl group. The core is substituted with a 4-fluorophenyl group, a 4-(1H-tetrazol-1-yl)phenyl group, and a 4-(2-oxo-2-(prop-1-en-1-yl)oxy)phenyl group.</p>

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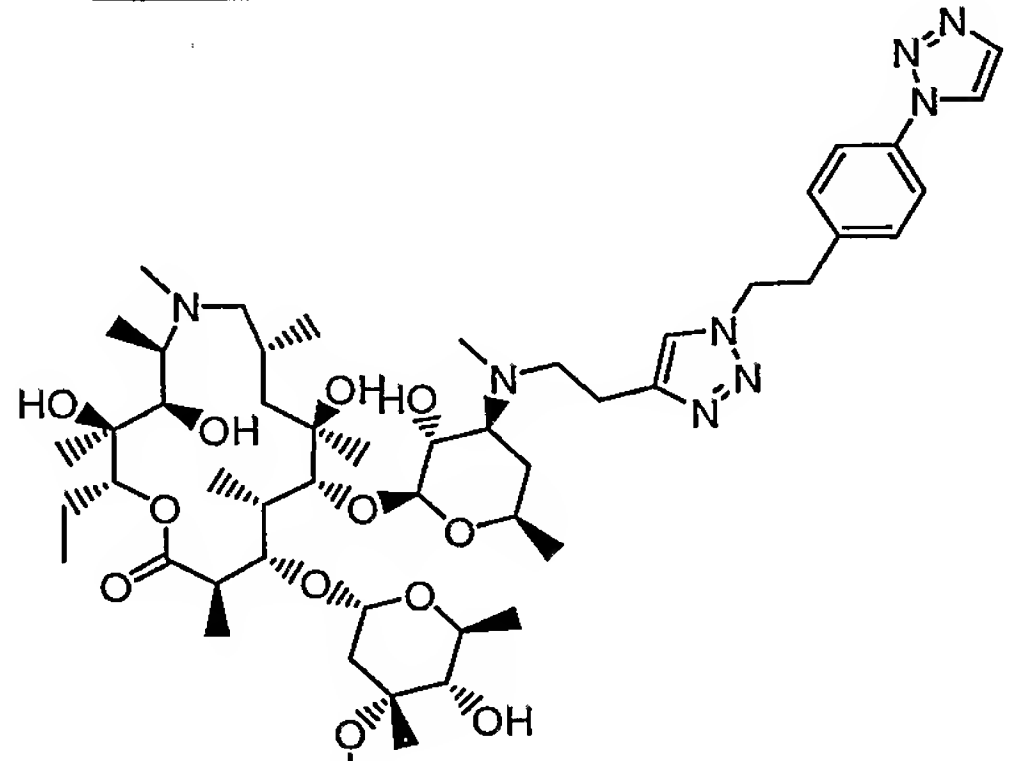
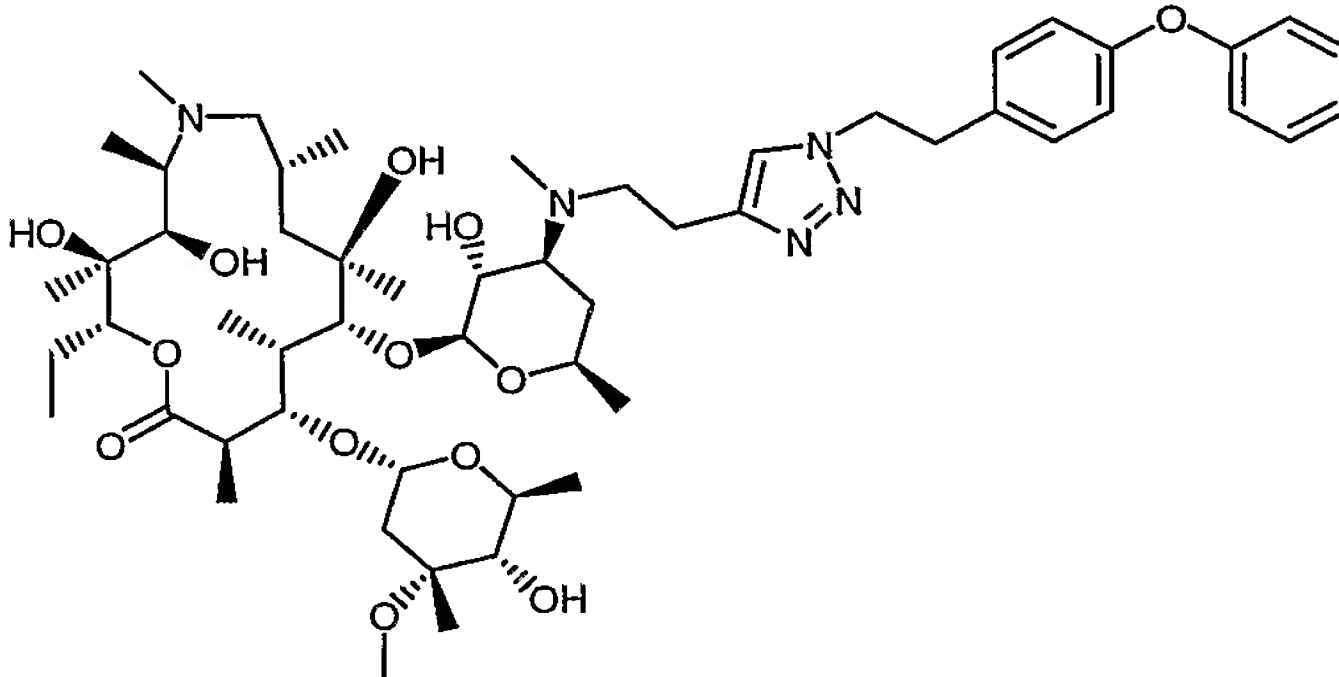
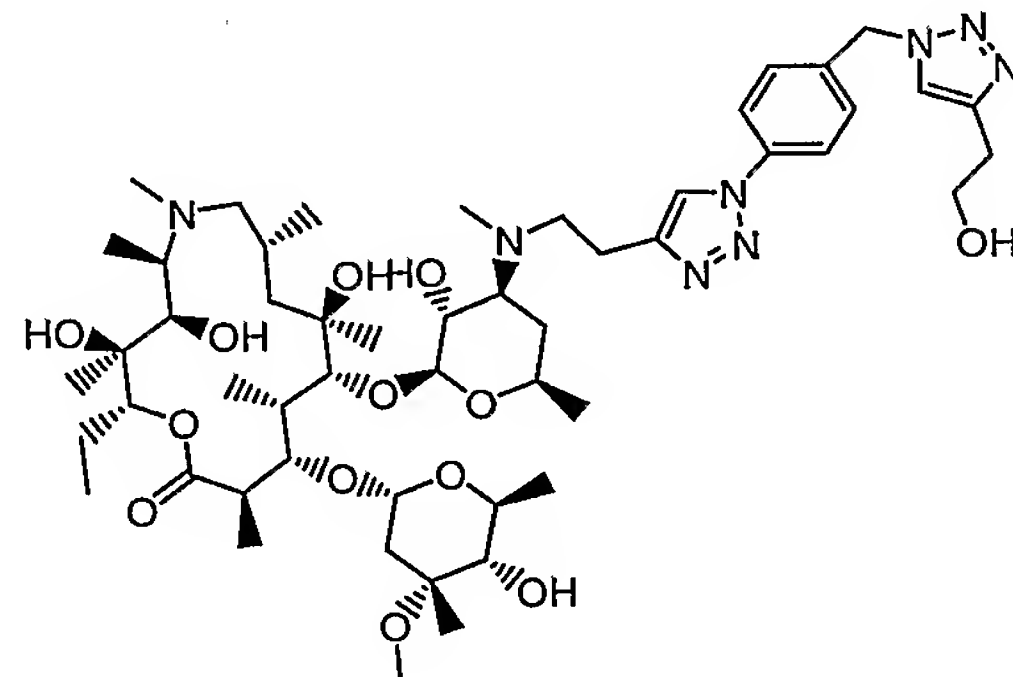
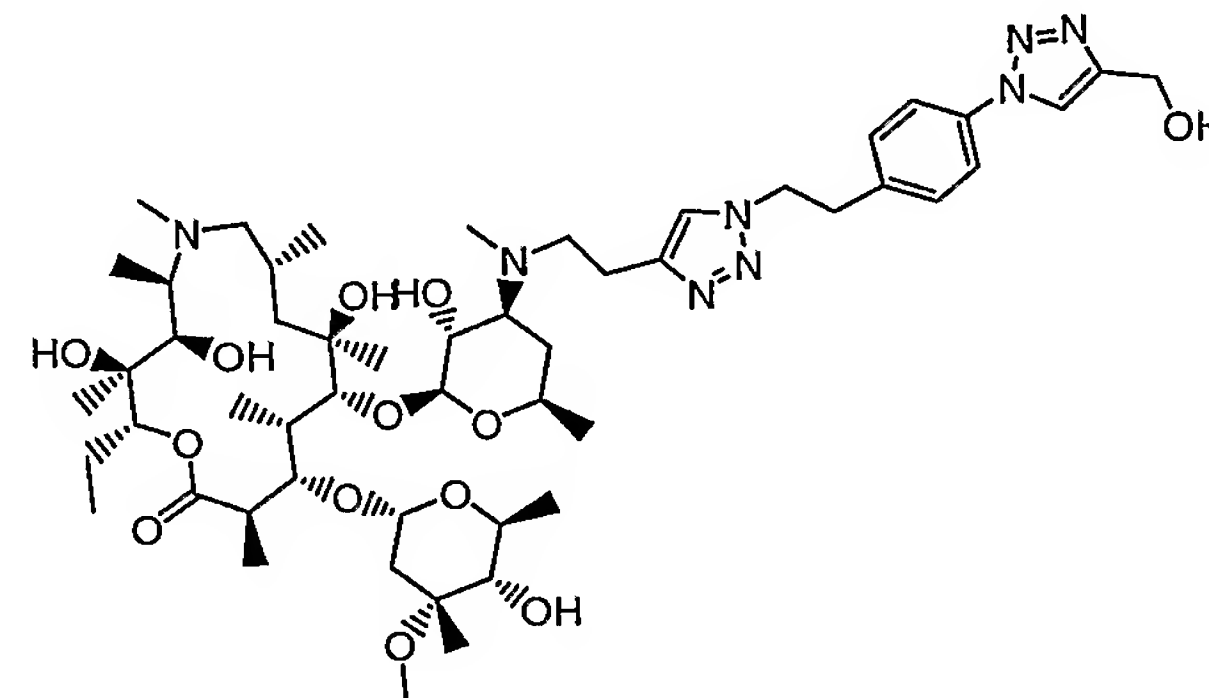
115	 <p>Chemical structure 115 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a carbonyl group. The molecule is substituted with a 4-fluorophenyl group via an amide linkage, a 1,2,4-triazole ring, and a 1,3-dioxane ring.</p>
116	 <p>Chemical structure 116 is a complex molecule, similar to 115, but with a different substituent on the phenyl ring (a methyl group instead of a fluorine atom).</p>

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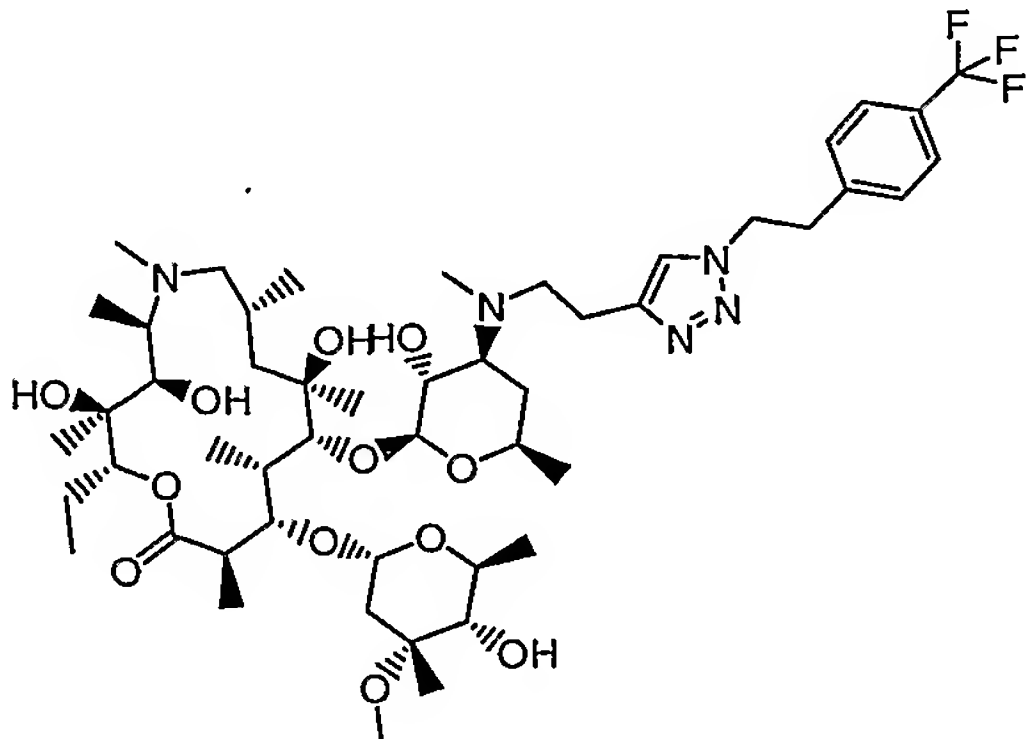
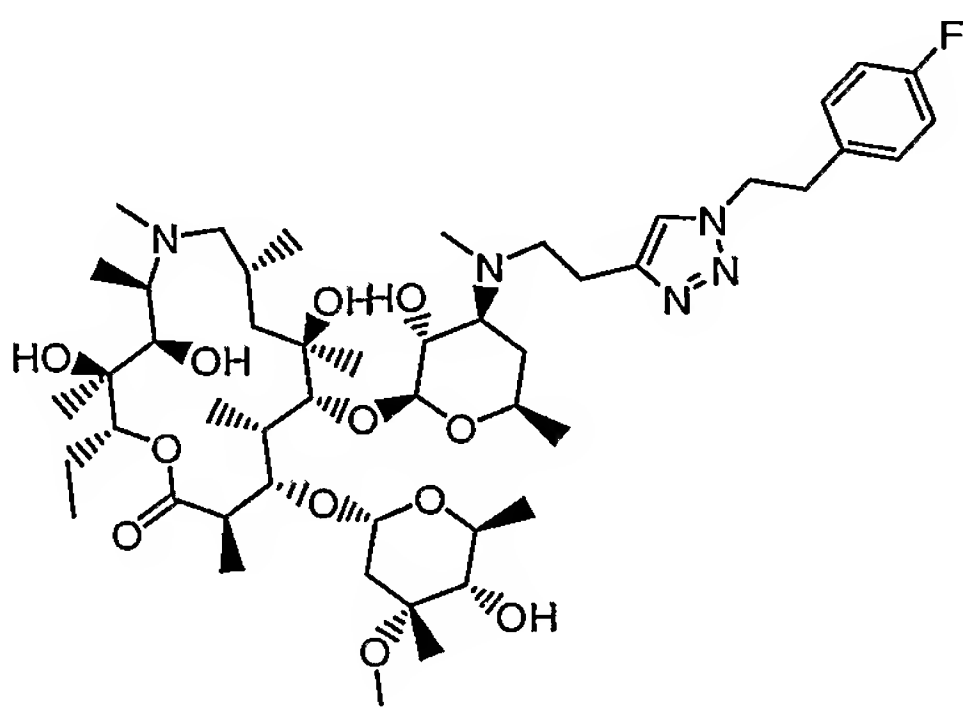
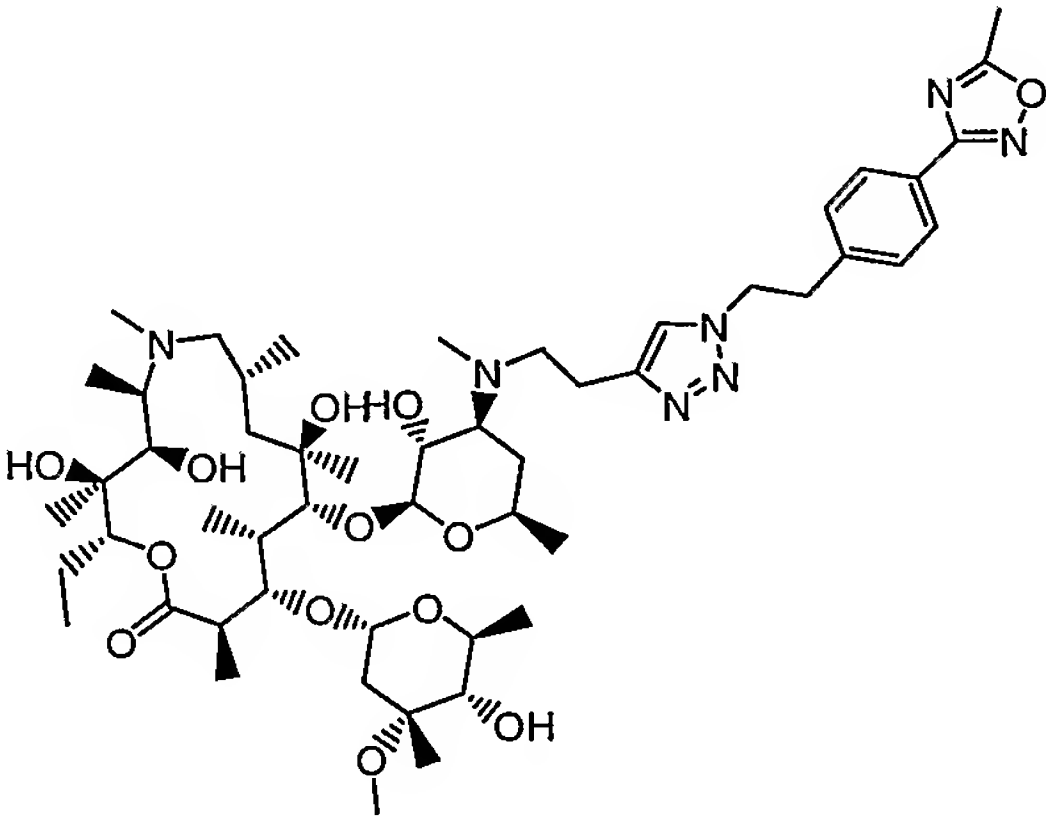
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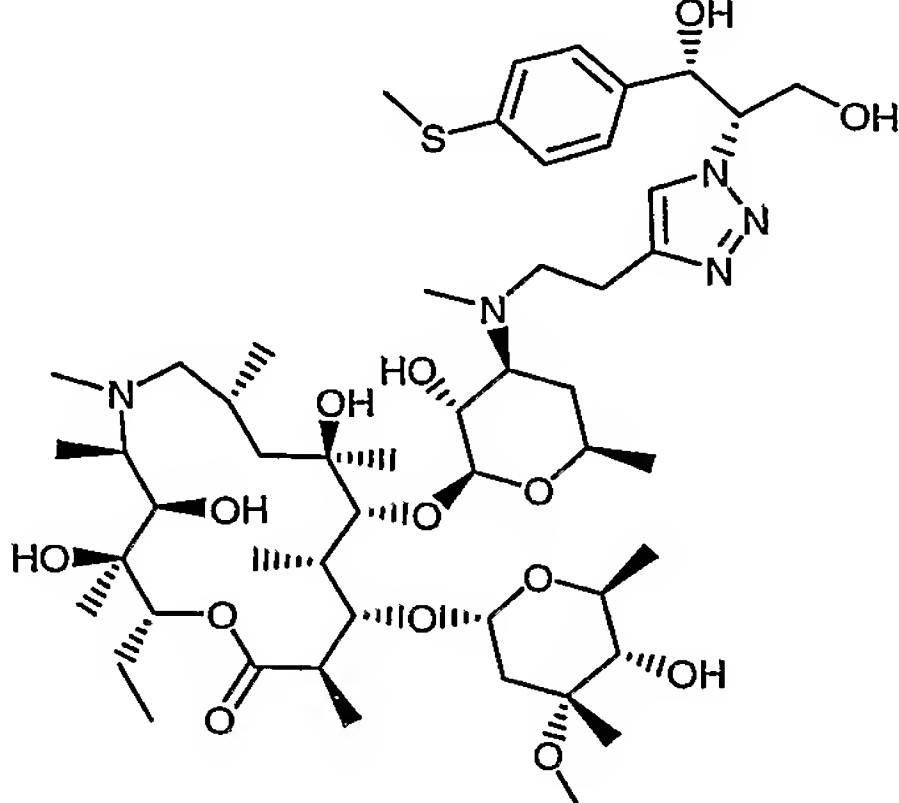
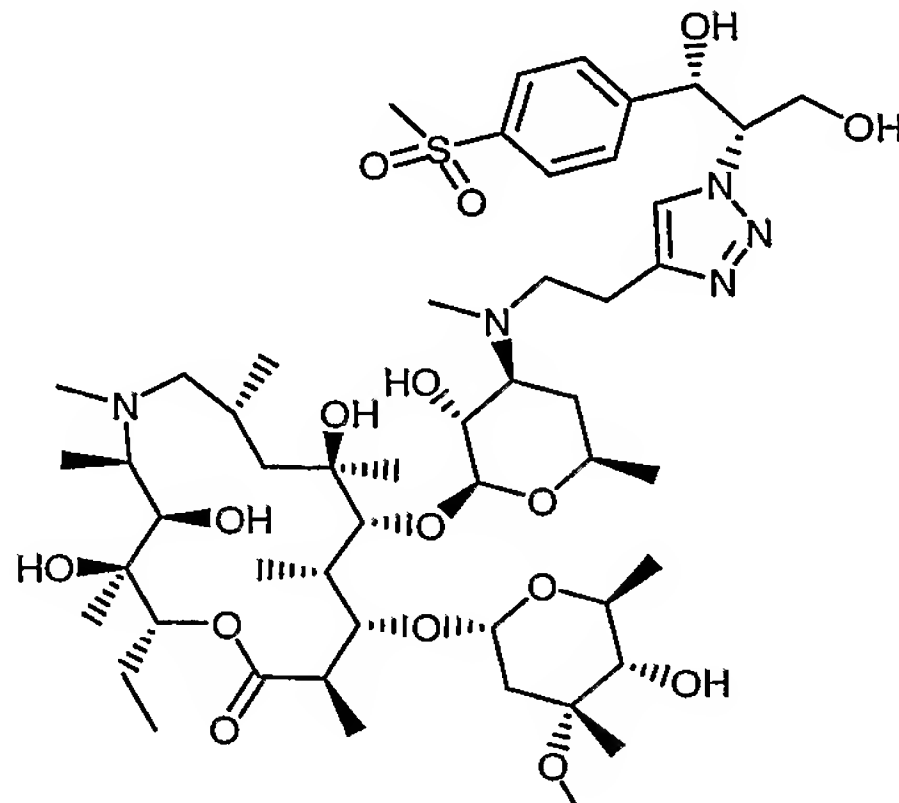
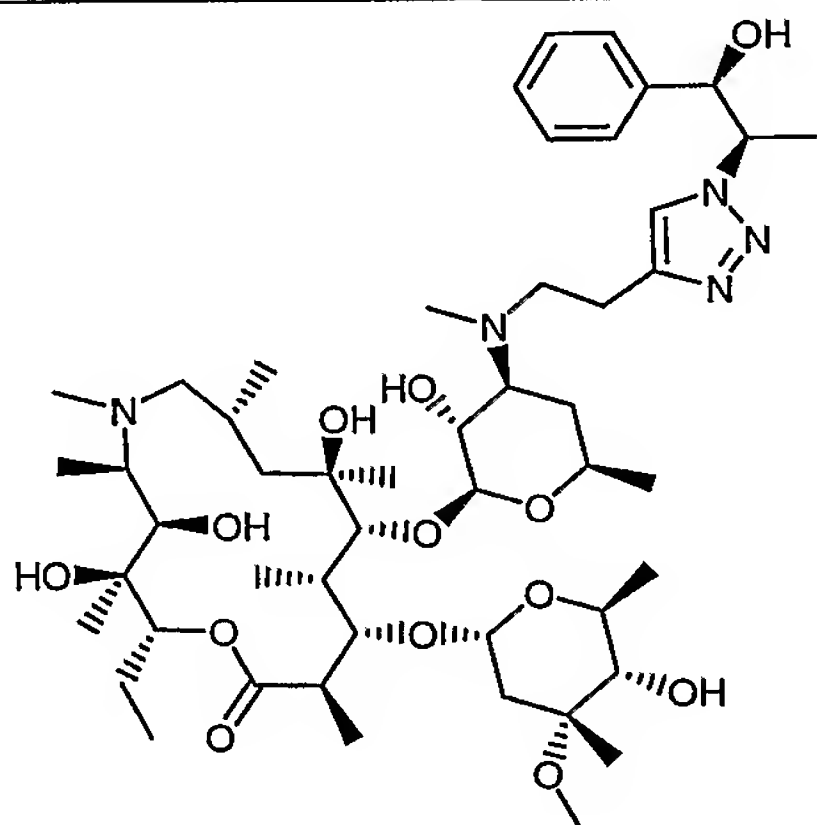
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124	
142	
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126	

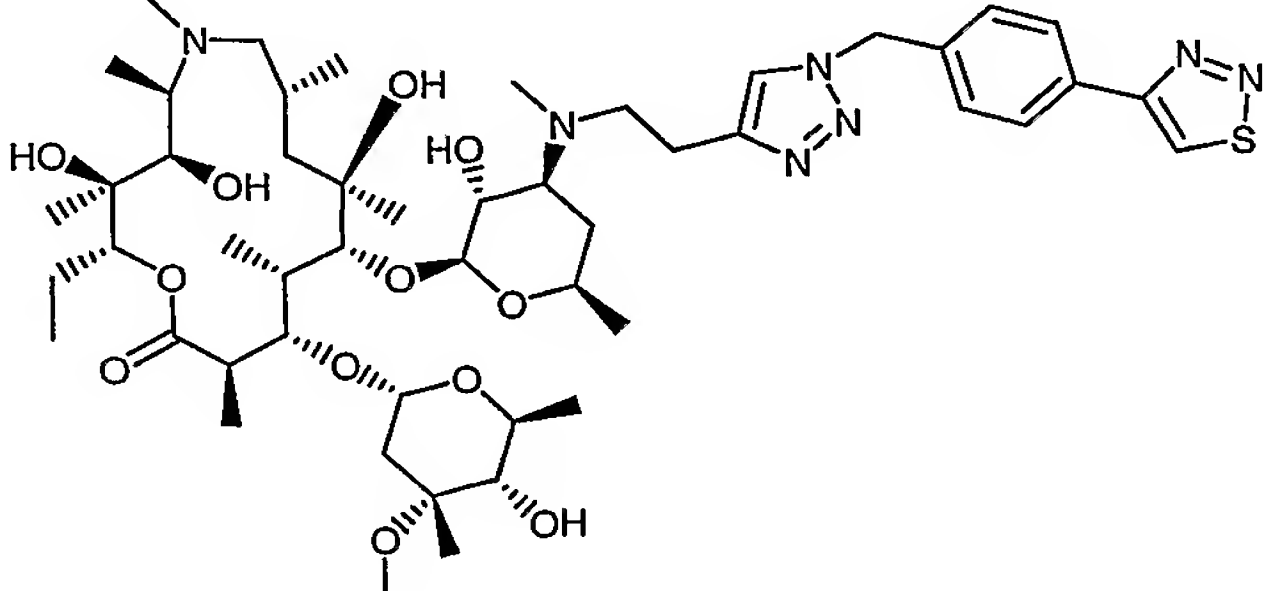
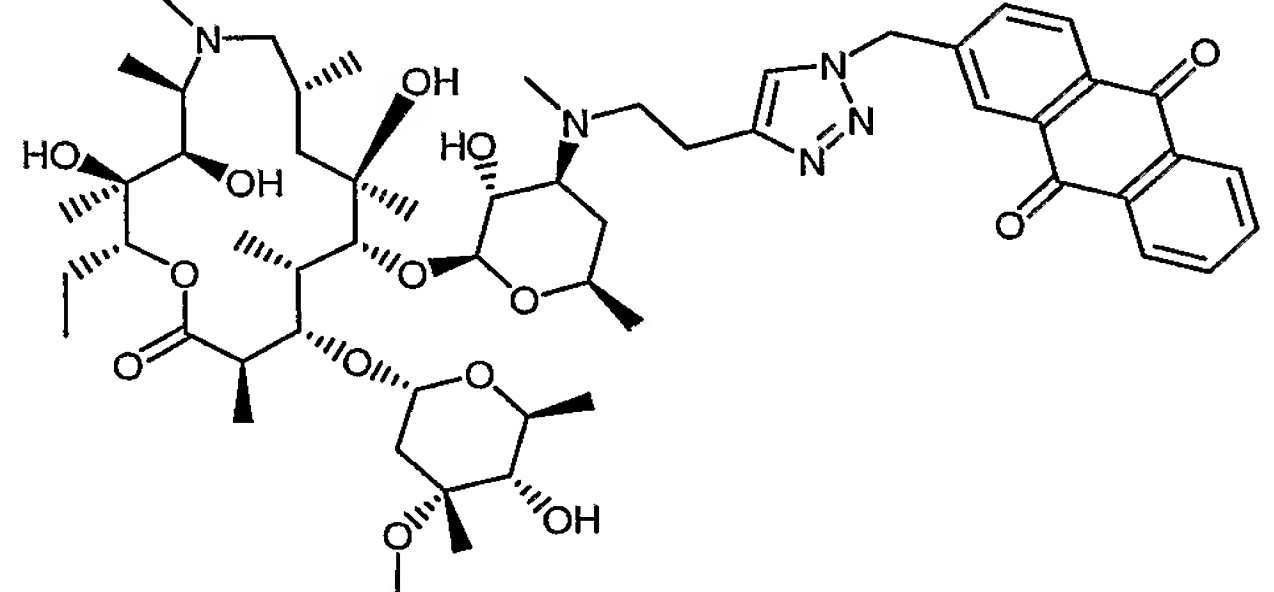
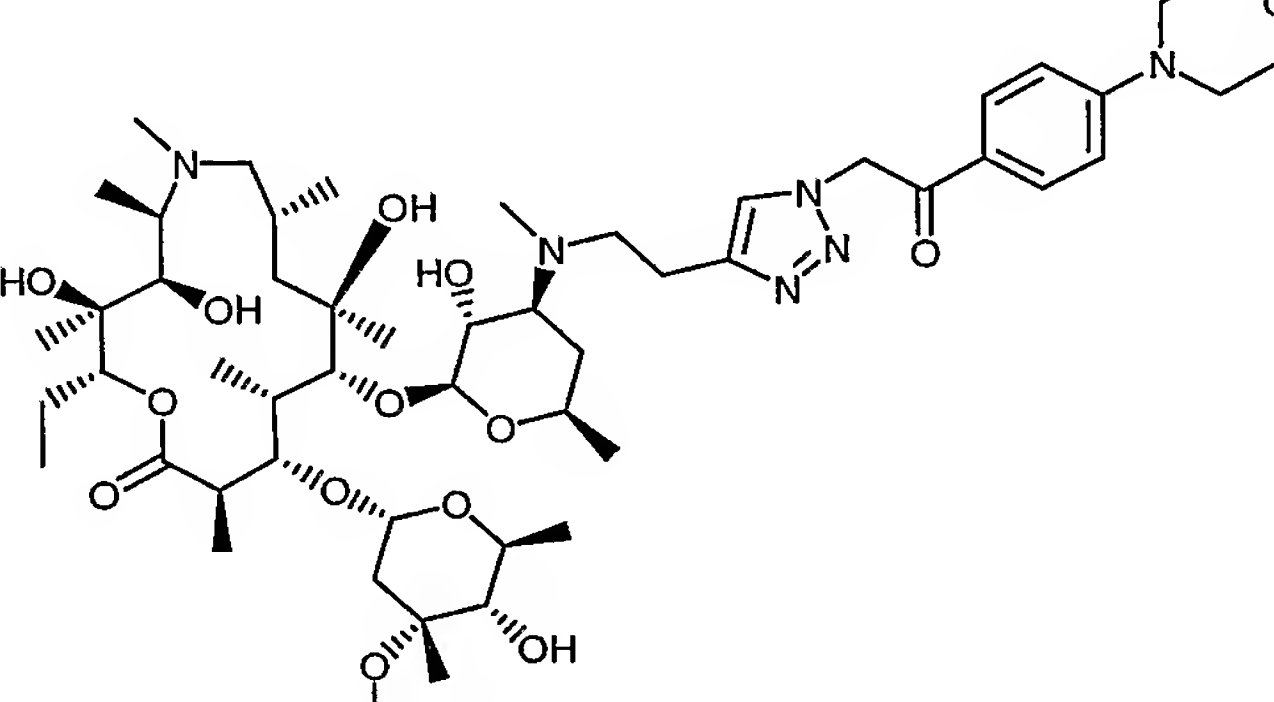
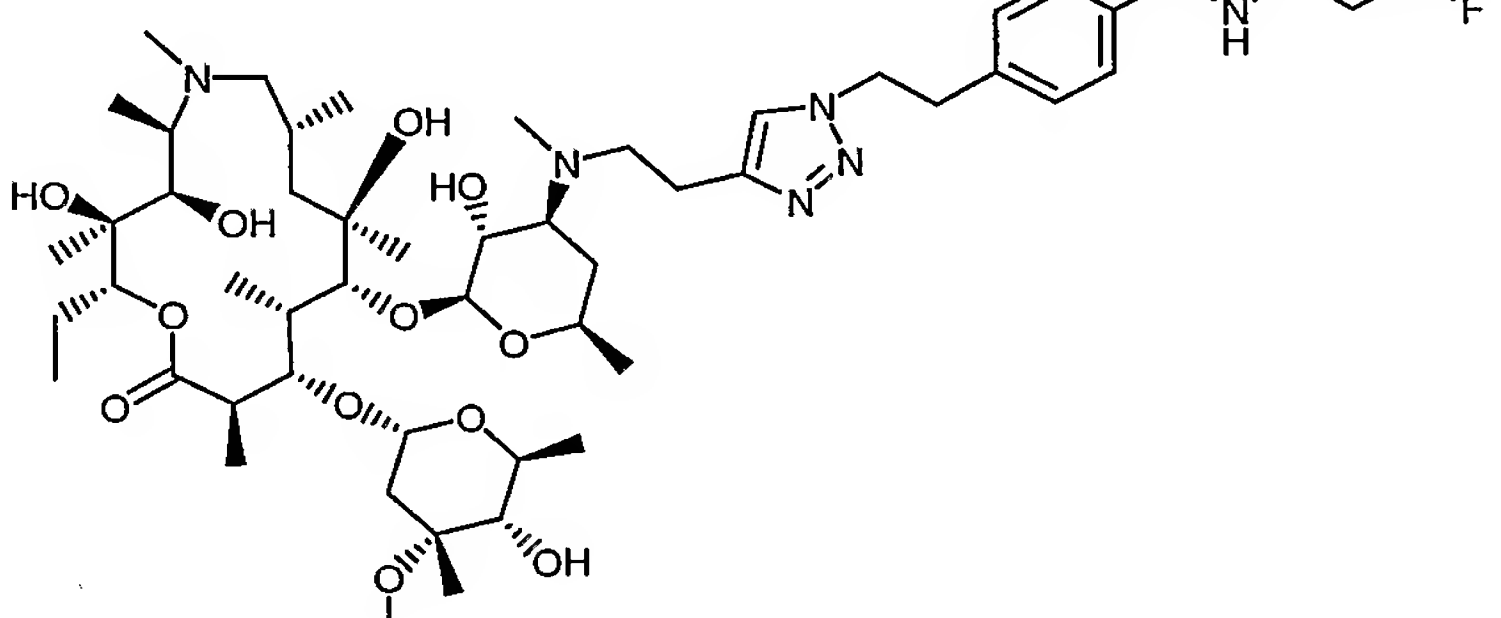
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129	 <p>Chemical structure 129 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a trifluoromethylphenyl group attached via a triazole linker.</p>
130	 <p>Chemical structure 130 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a fluorophenyl group attached via a triazole linker.</p>
131	 <p>Chemical structure 131 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a 4-methyl-1,2,4-oxadiazol-5-ylphenyl group attached via a triazole linker.</p>

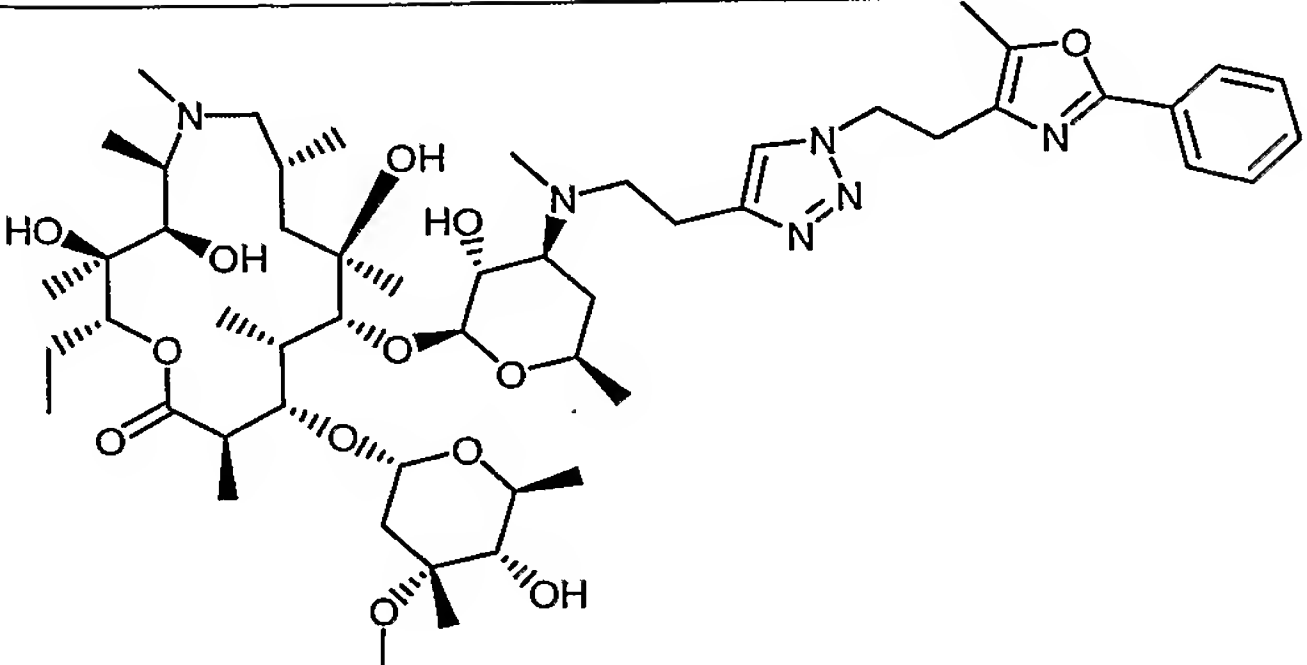
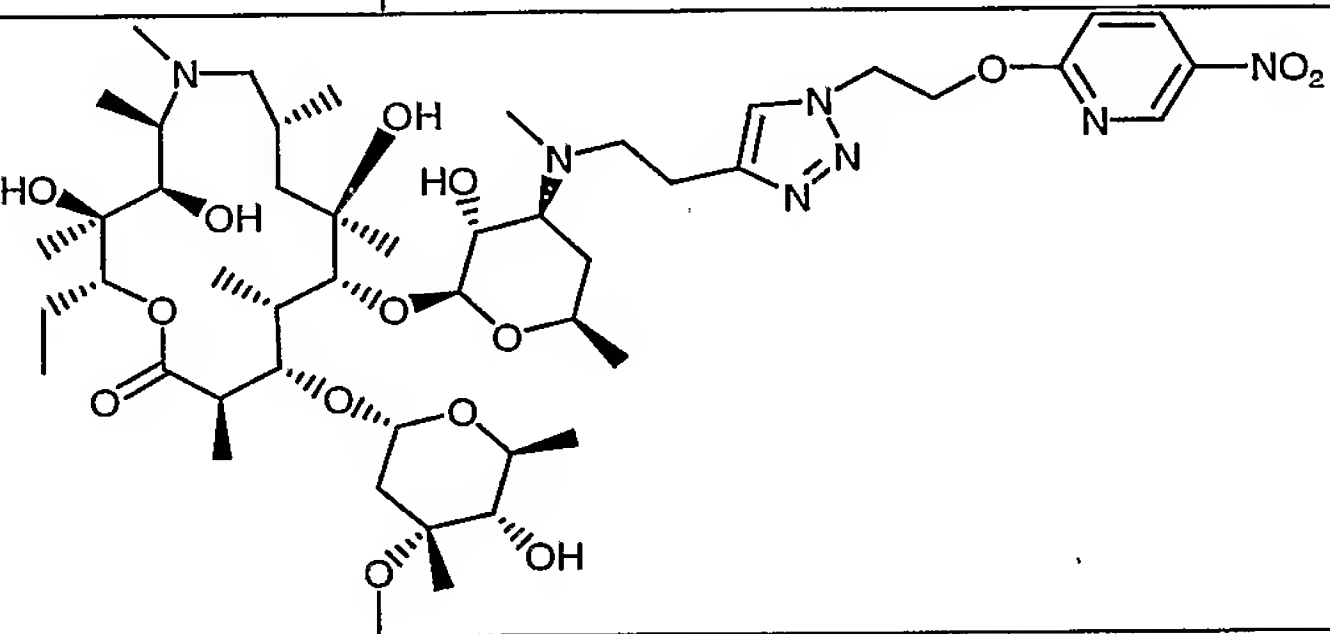
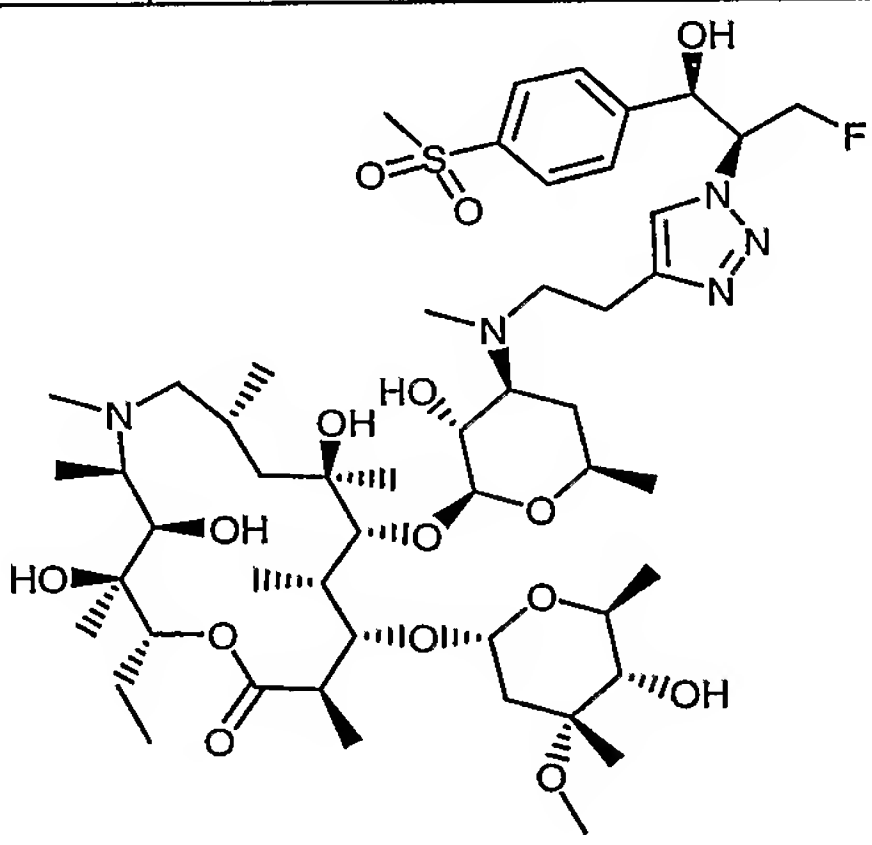
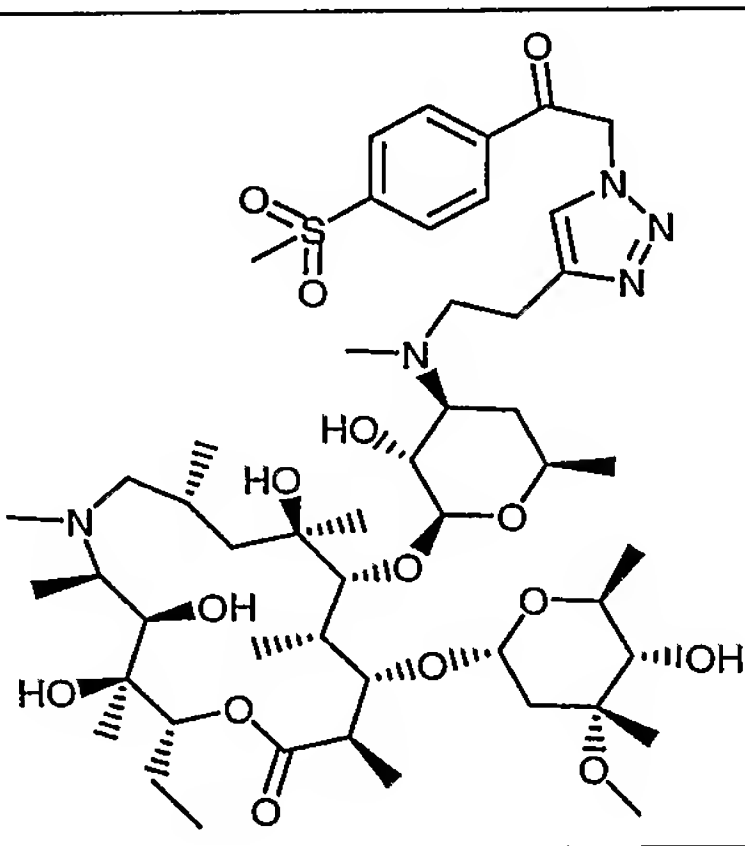
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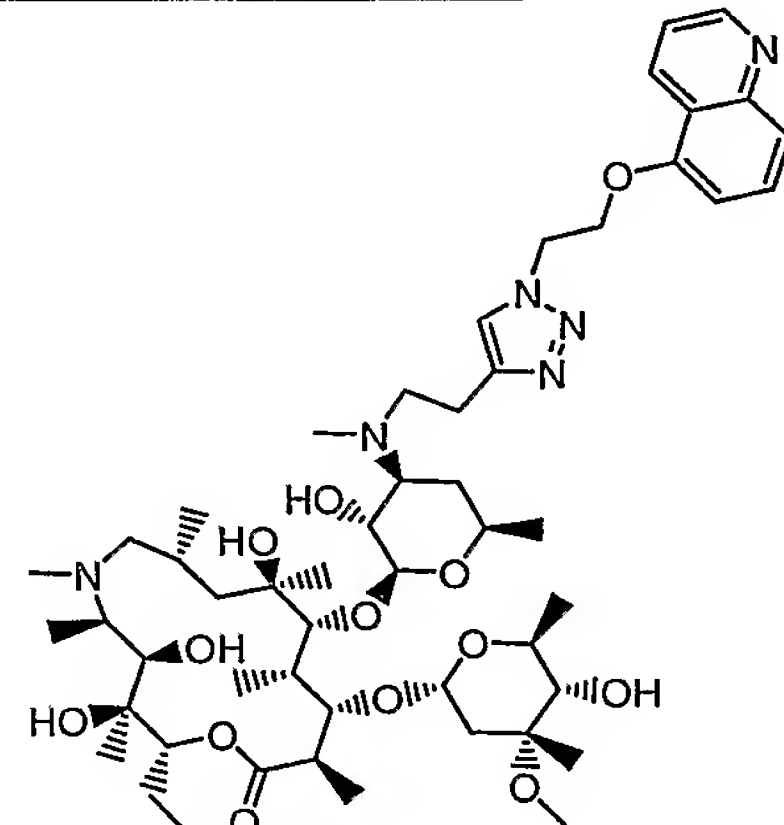
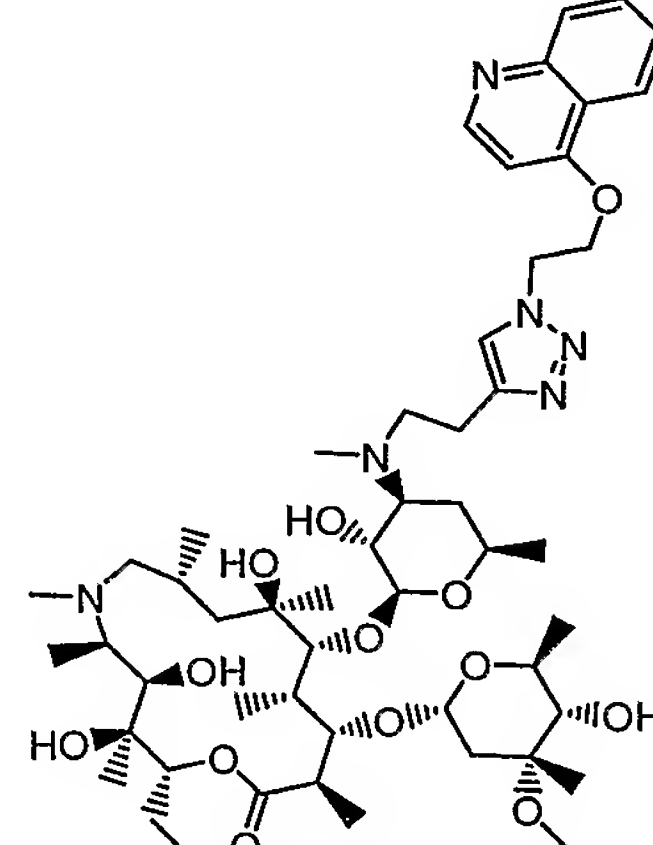
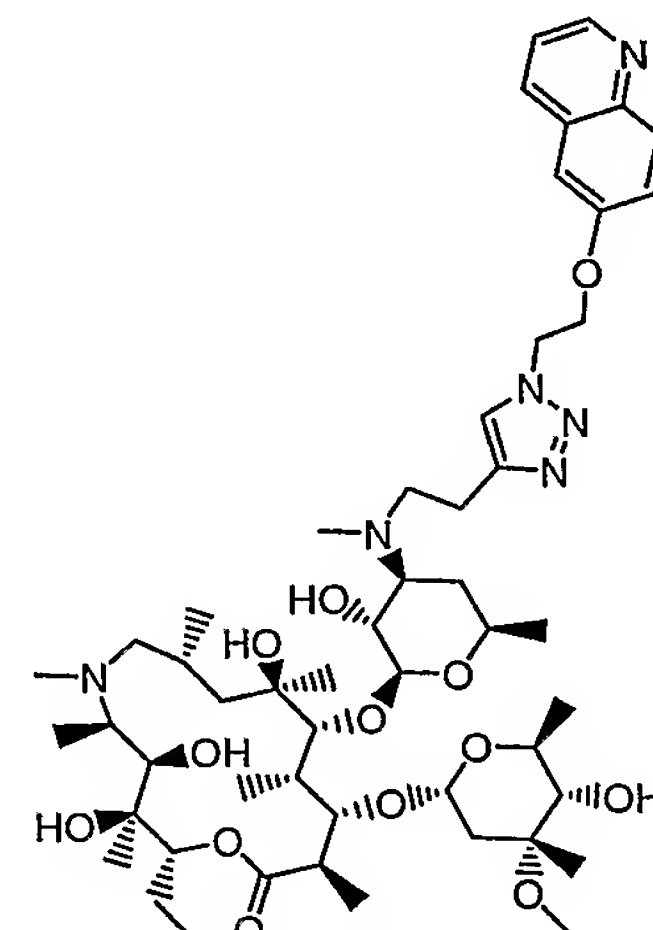
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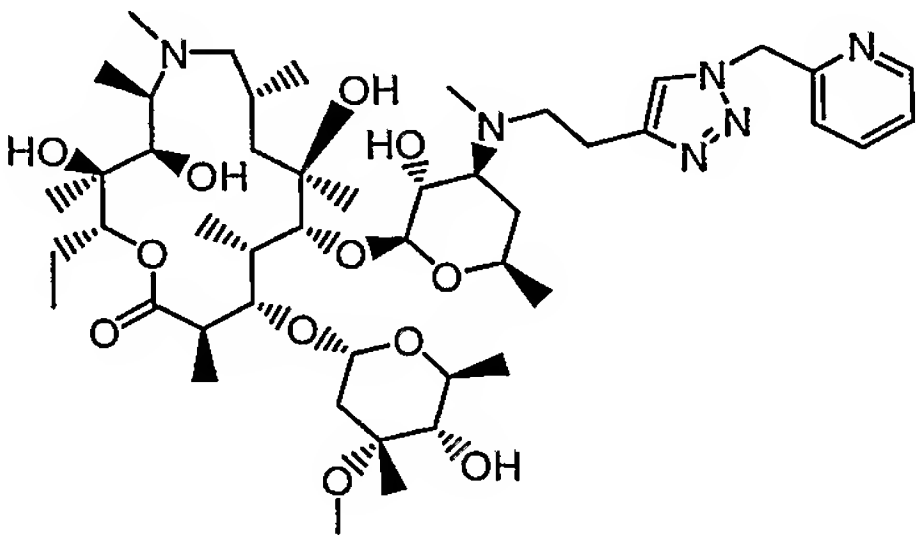
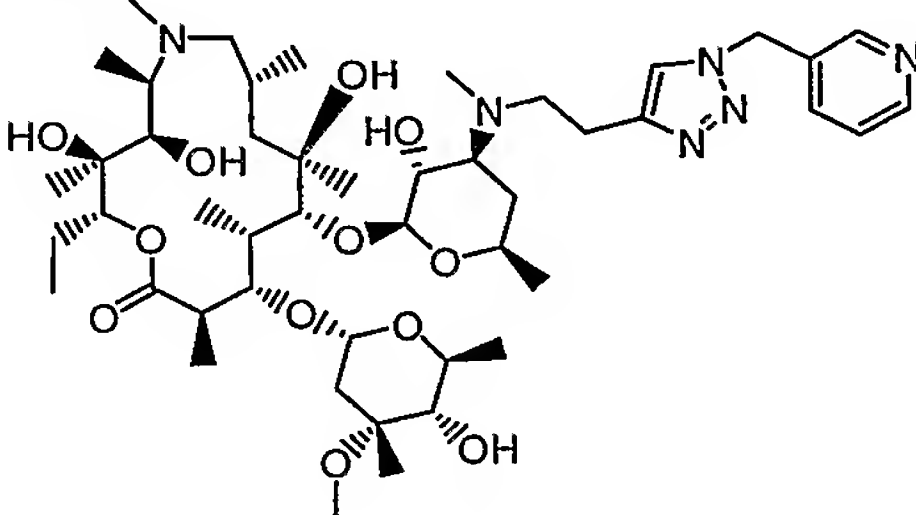
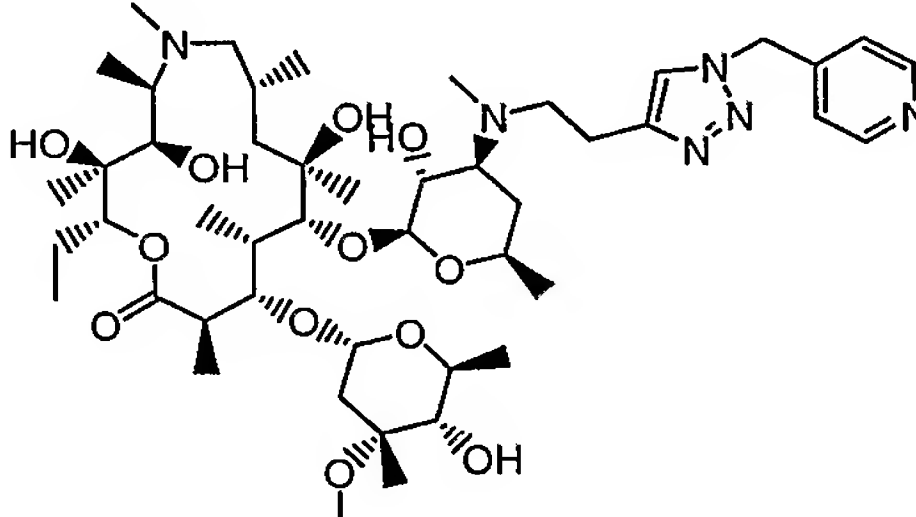
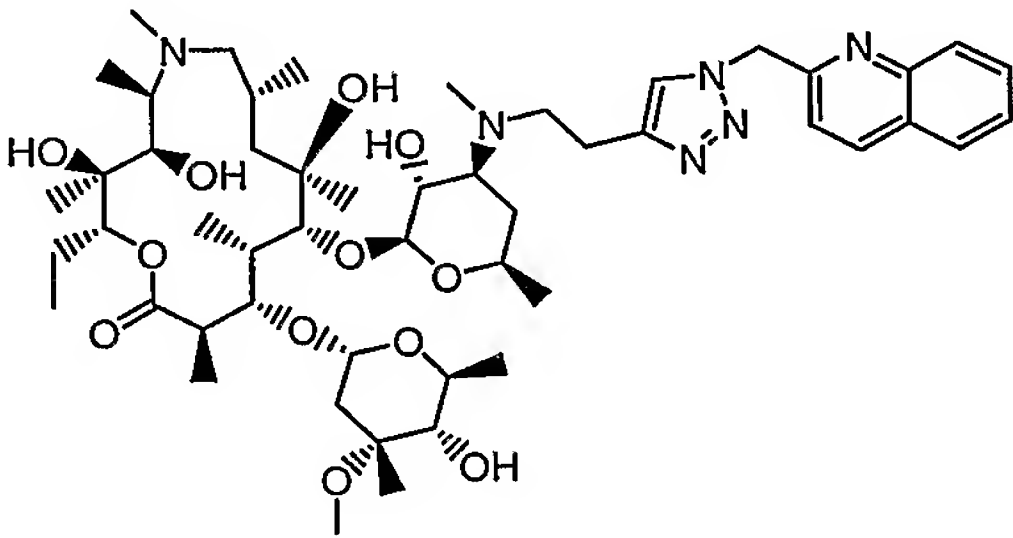
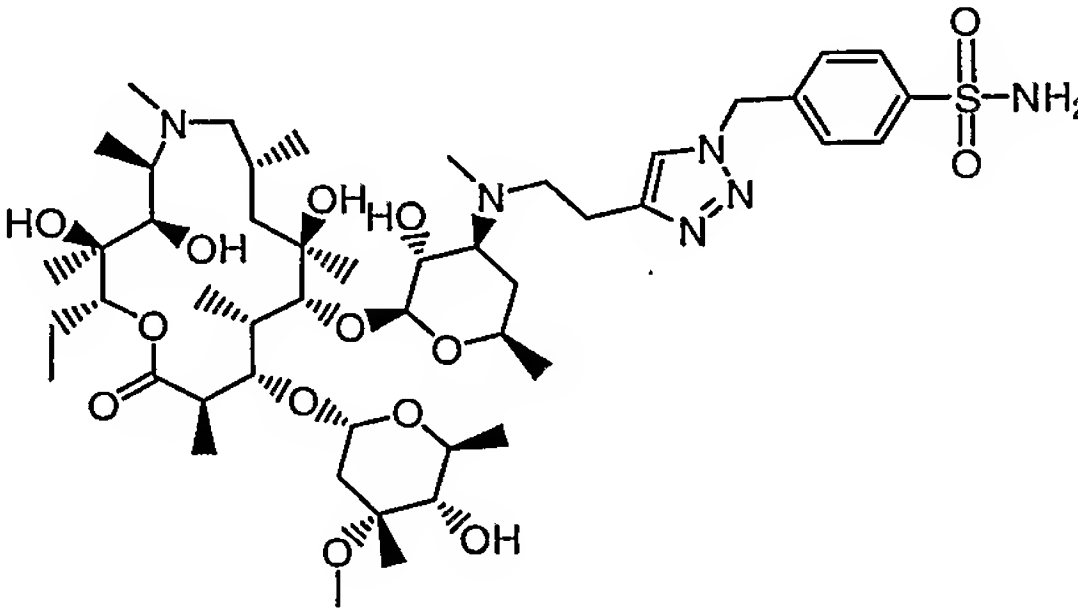
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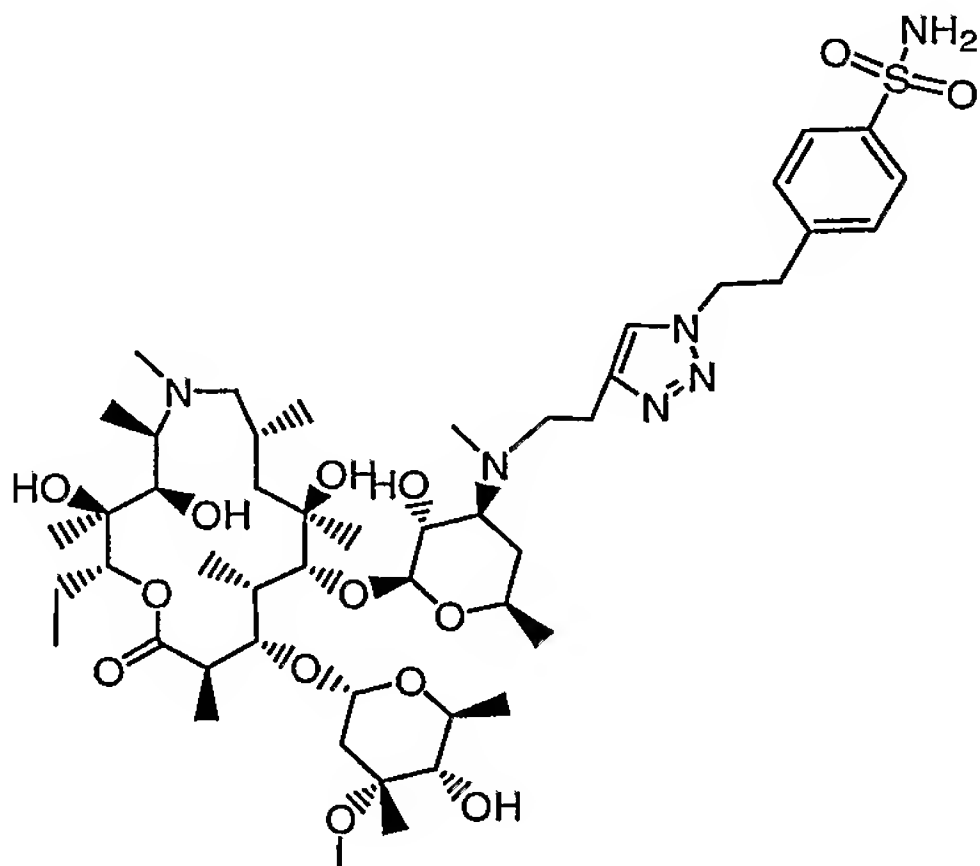
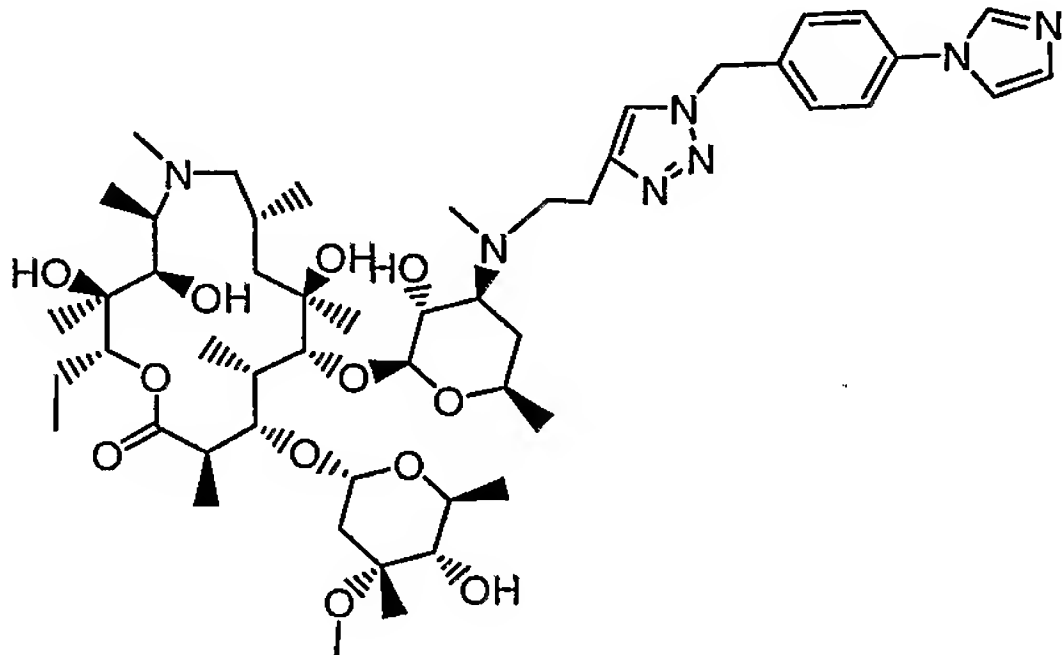
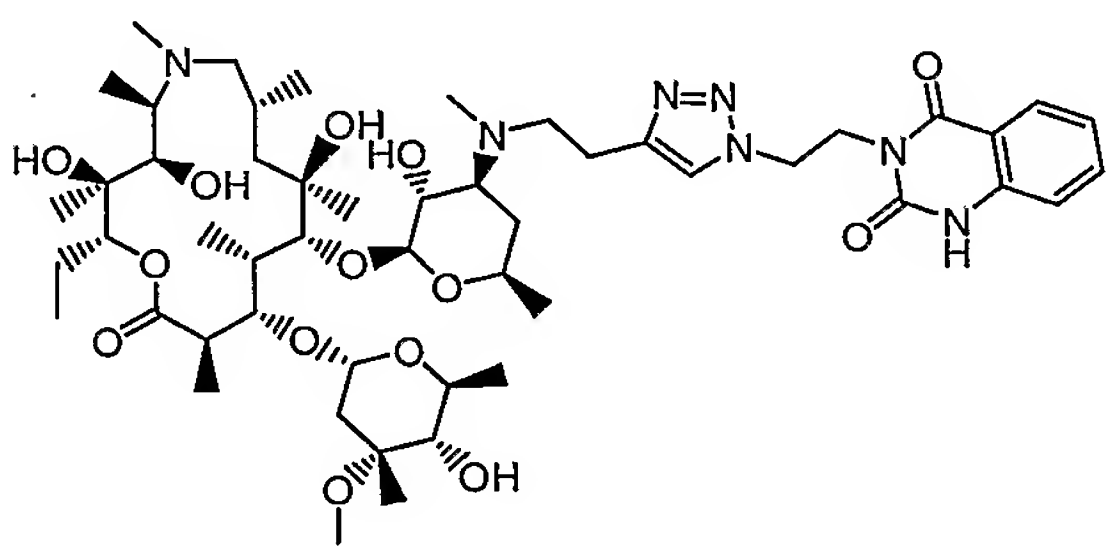
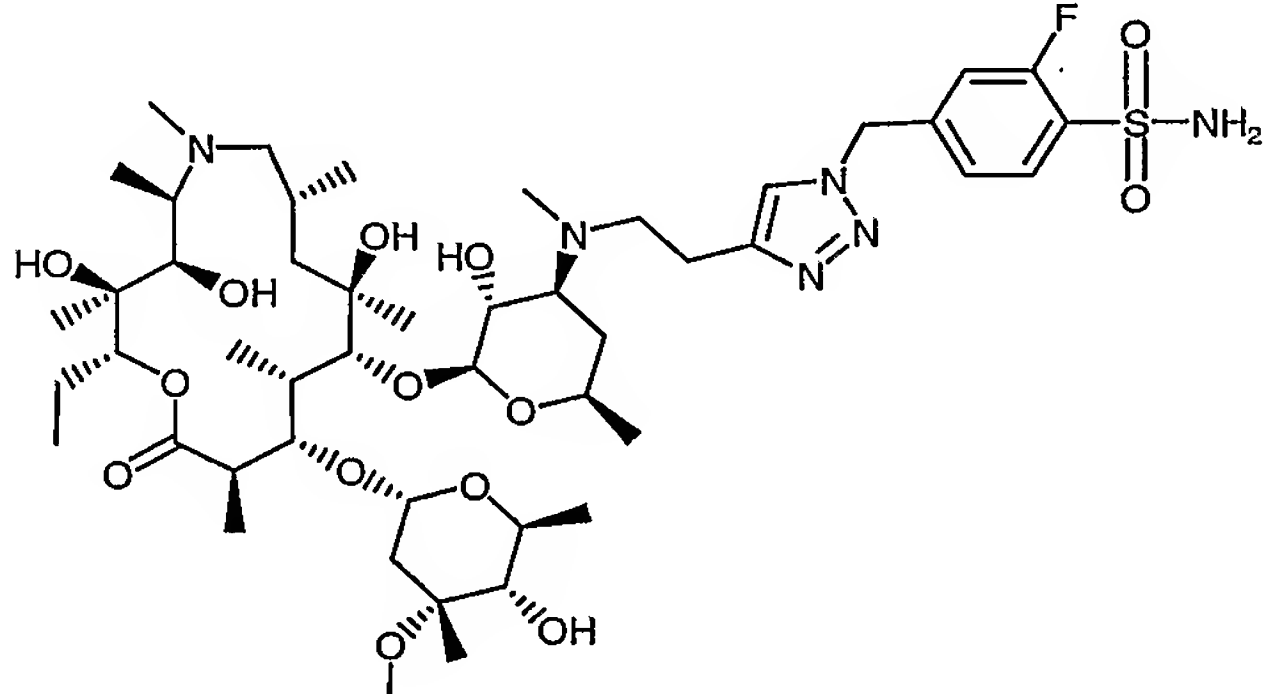
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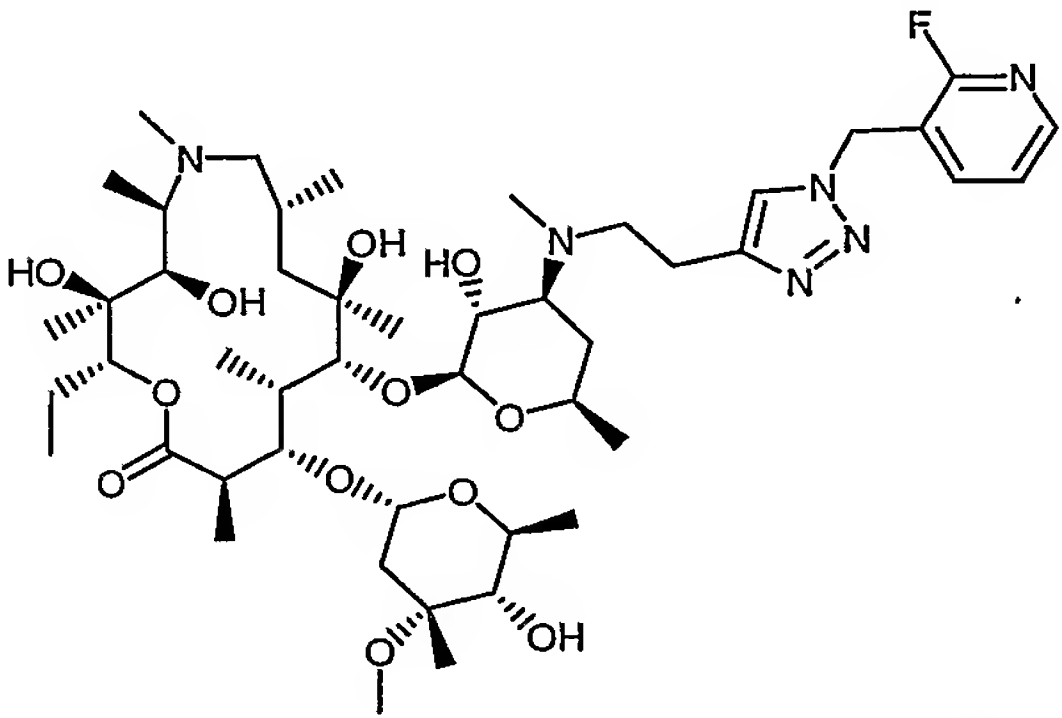
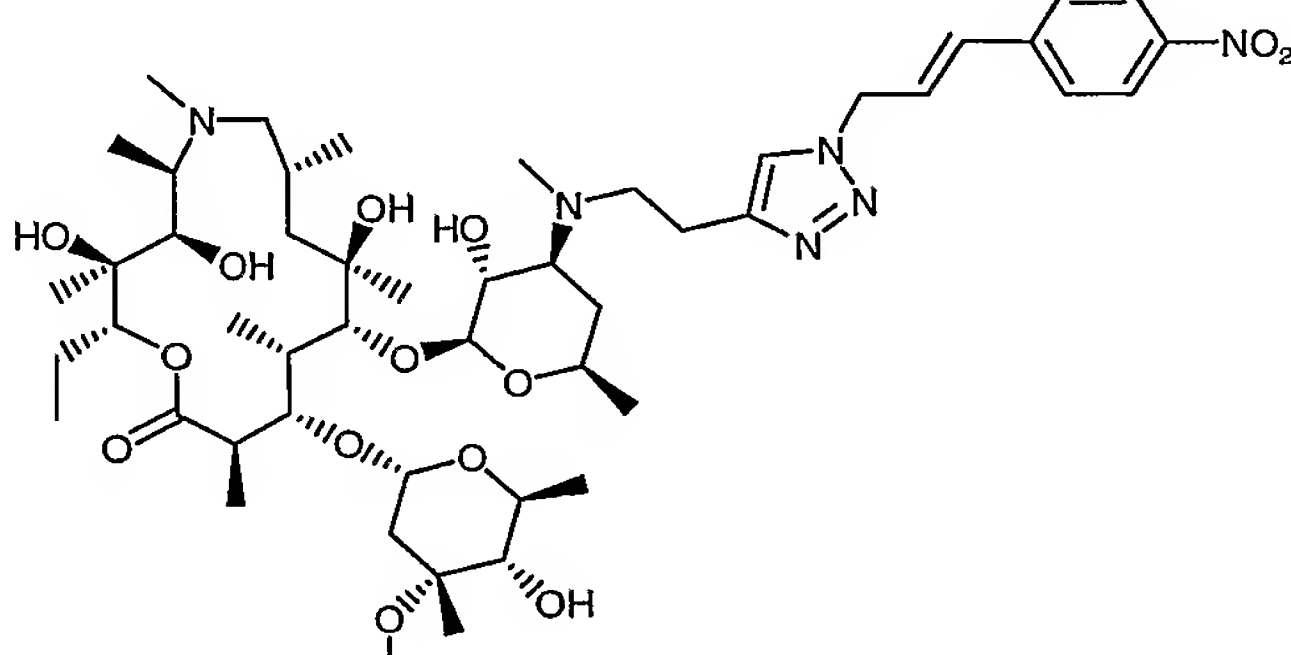
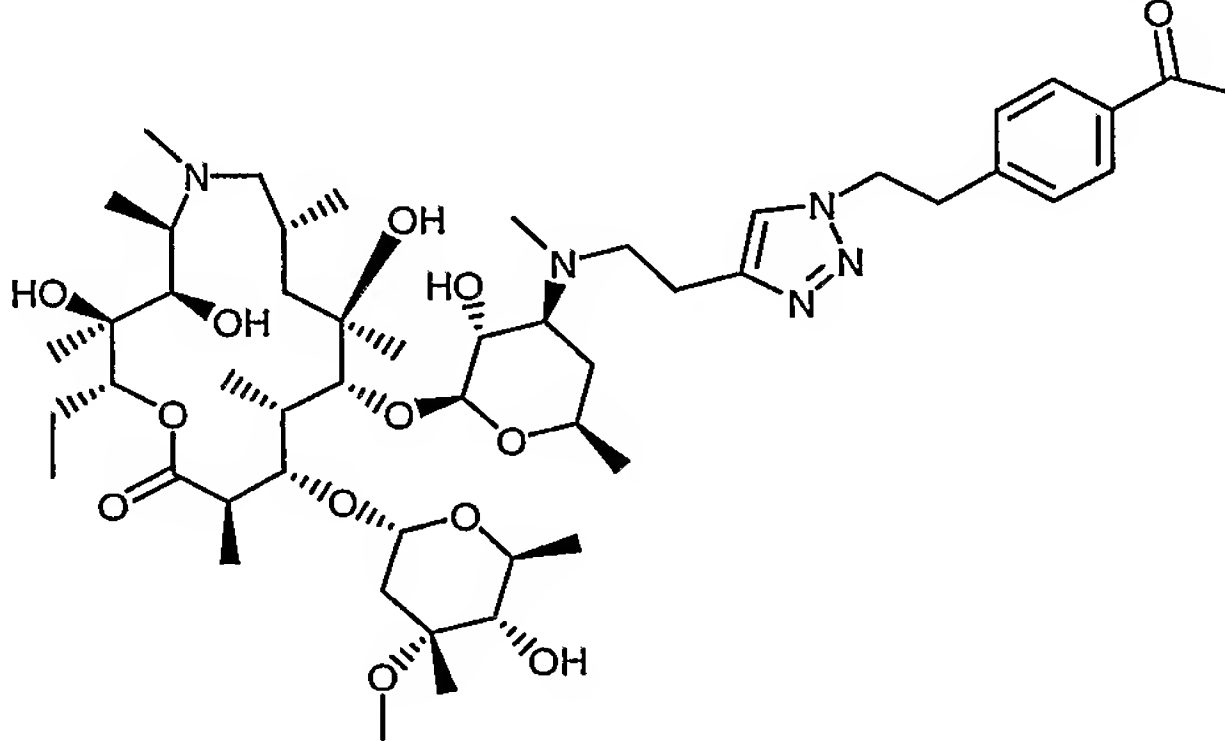
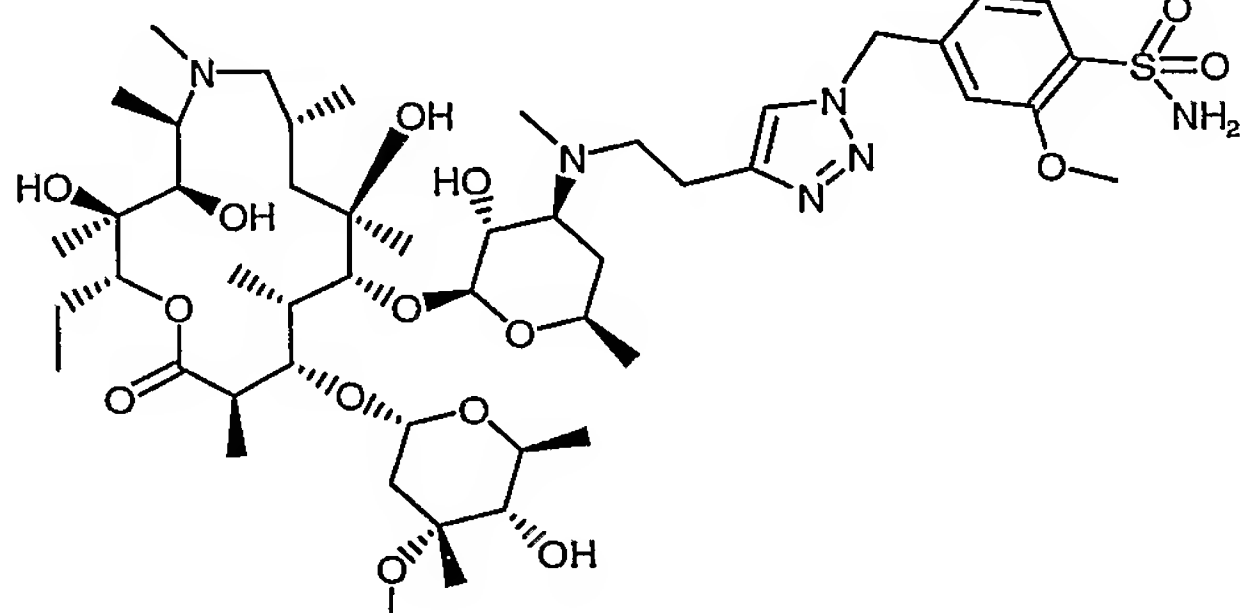
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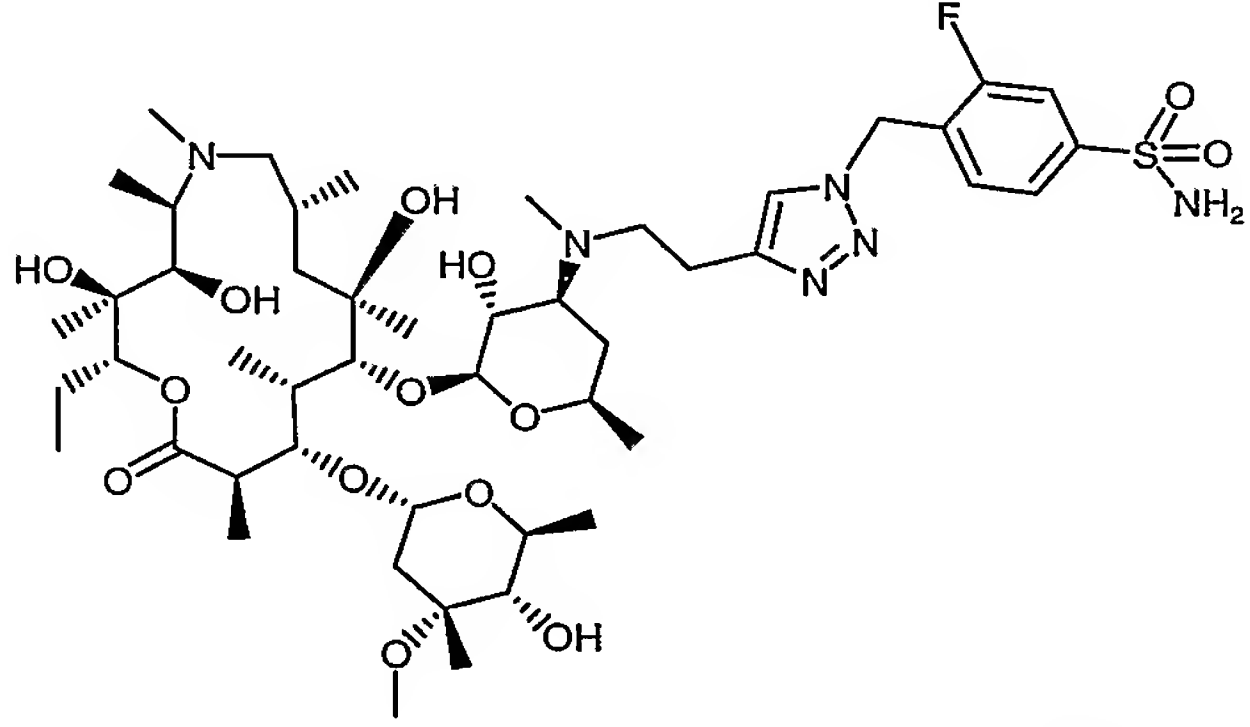
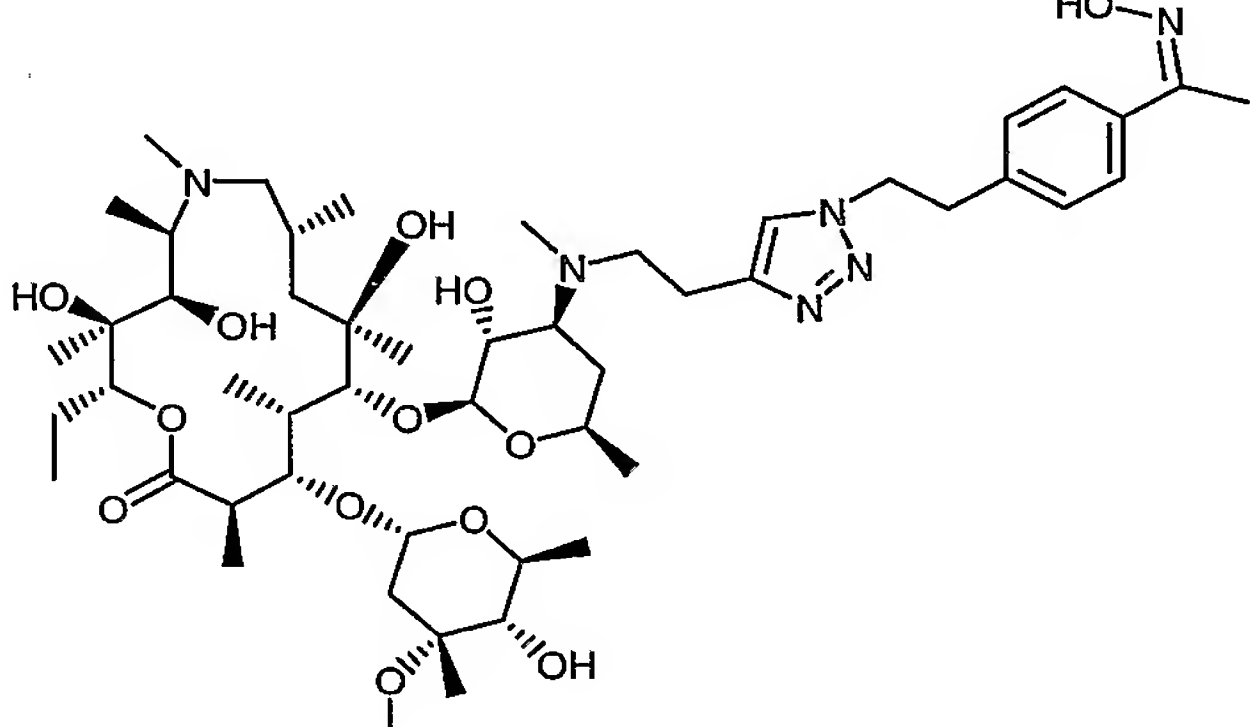
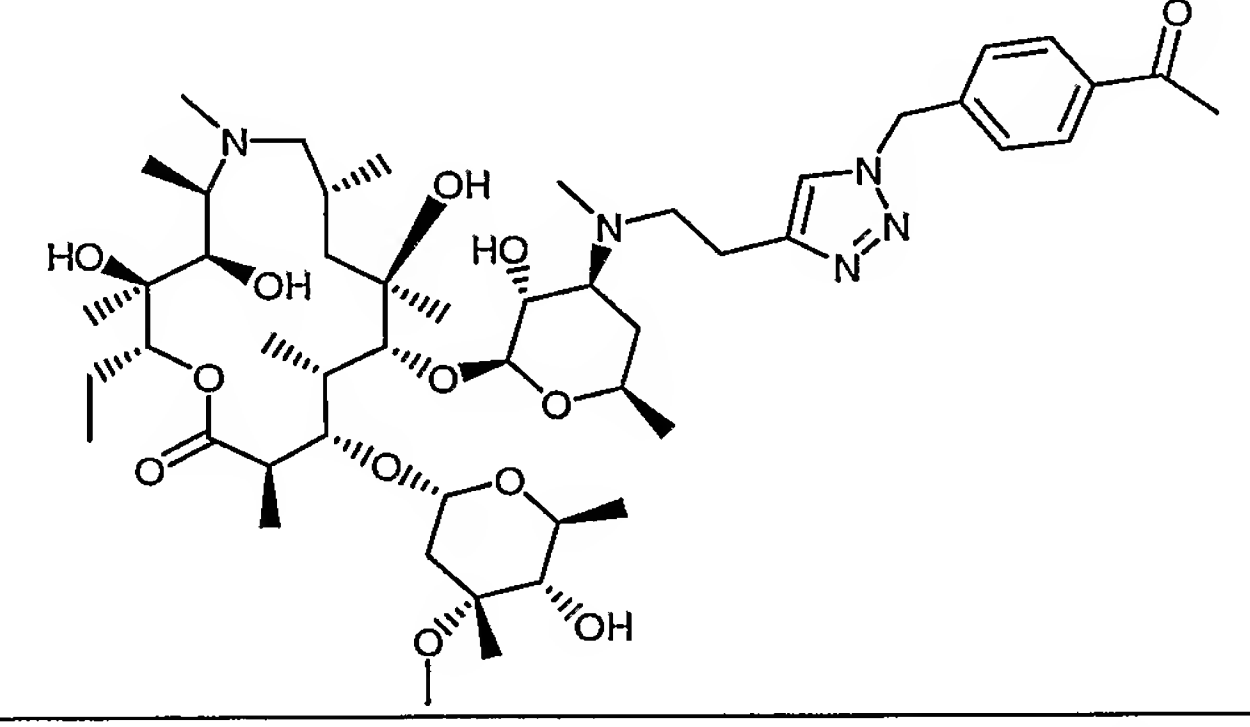
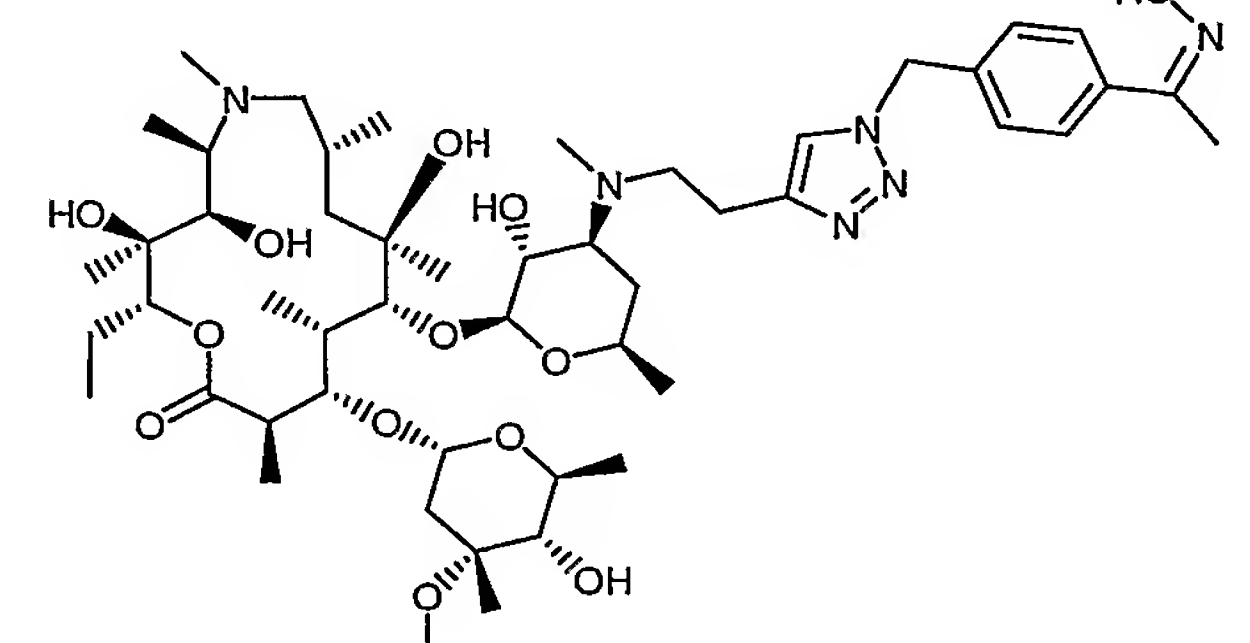
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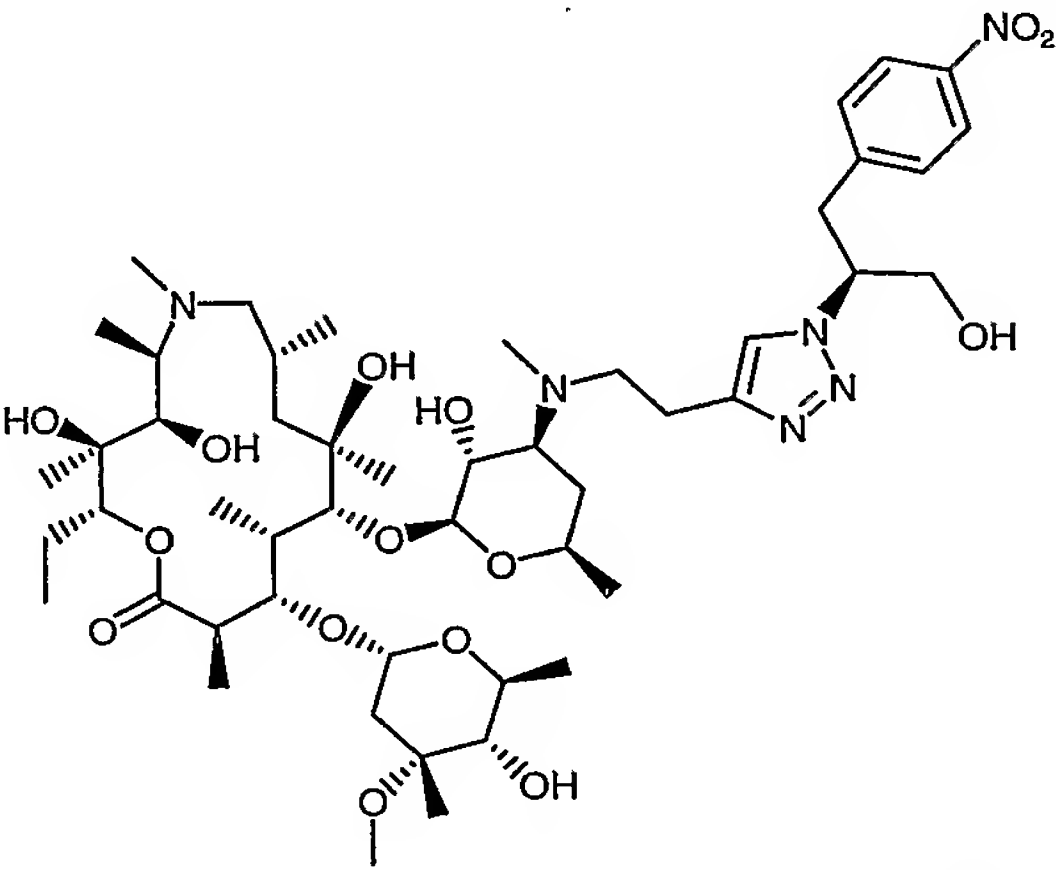
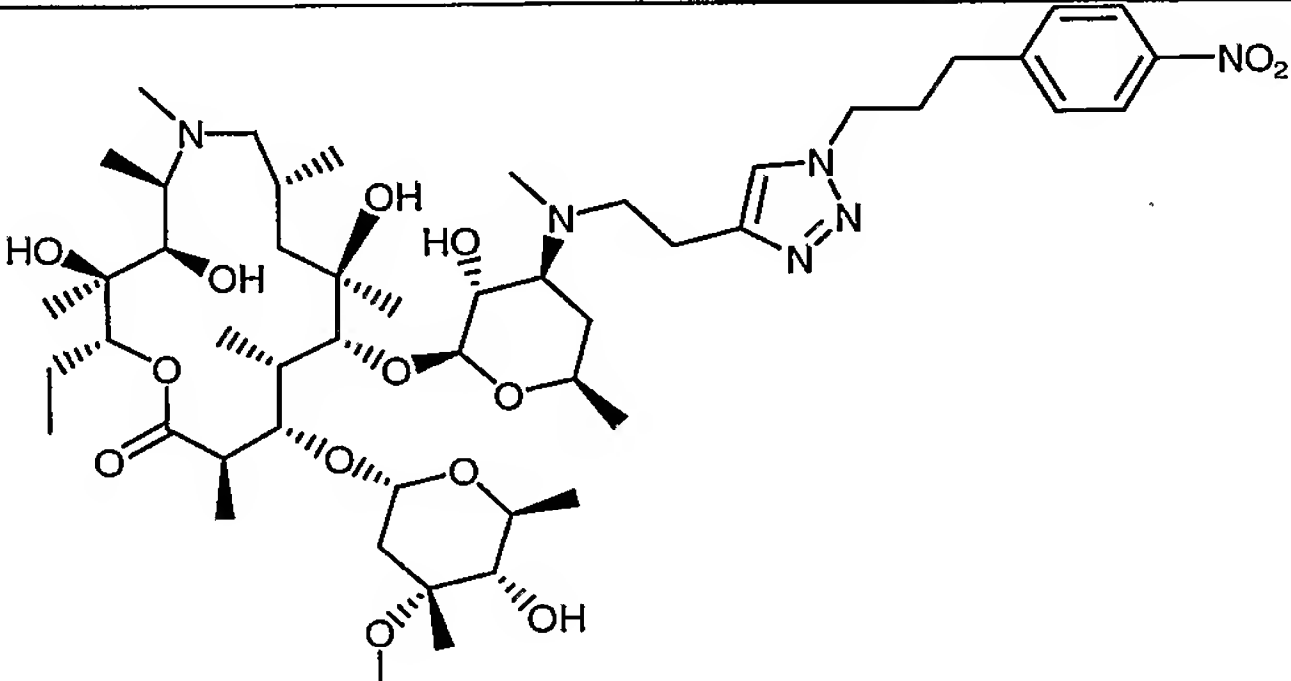
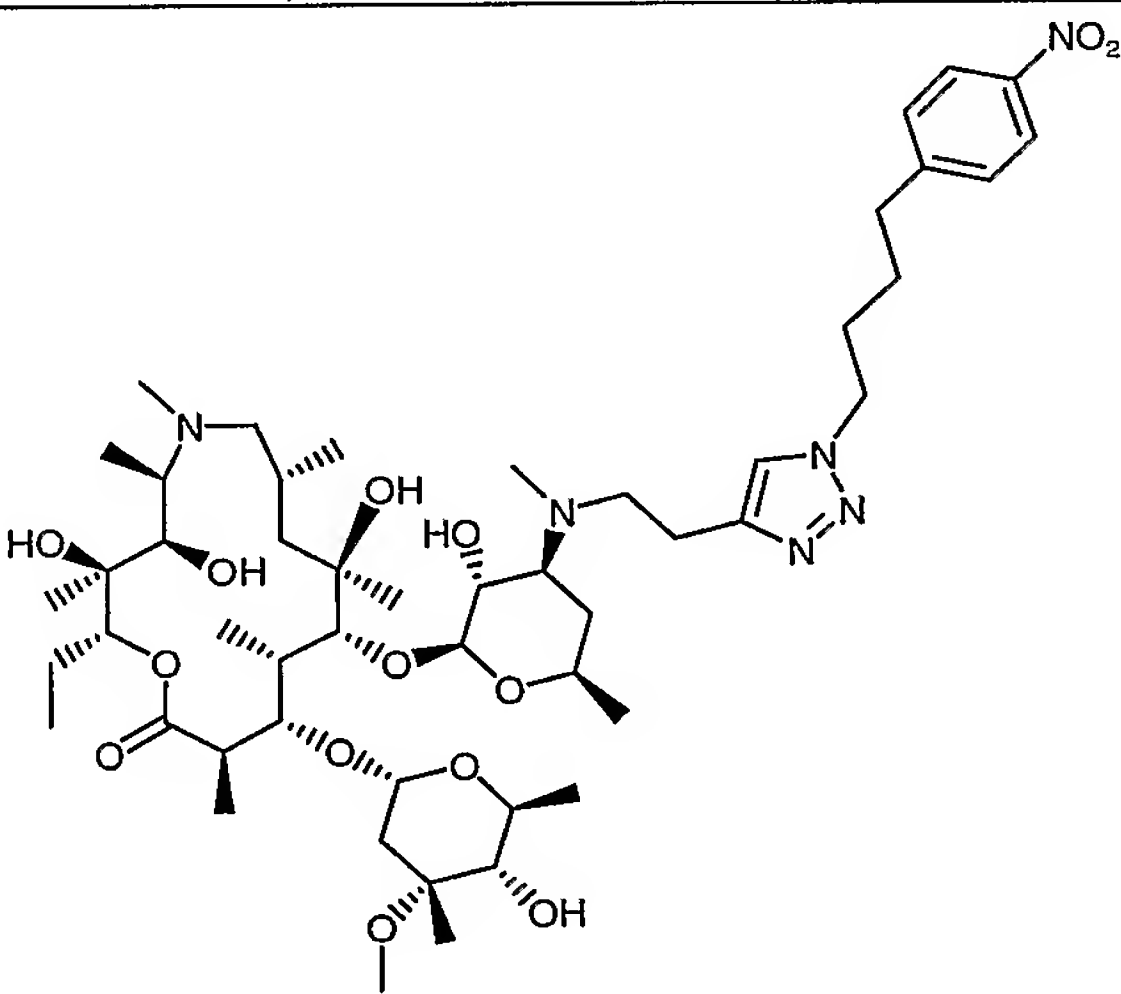
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156	 <p>Chemical structure 156: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a sulfonamide group attached via a triazole ring.</p>
157	 <p>Chemical structure 157: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a pyridine ring attached via a triazole ring.</p>
158	 <p>Chemical structure 158: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a benzimidazole ring attached via a triazole ring.</p>
159	 <p>Chemical structure 159: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a fluorinated sulfonamide group attached via a triazole ring.</p>

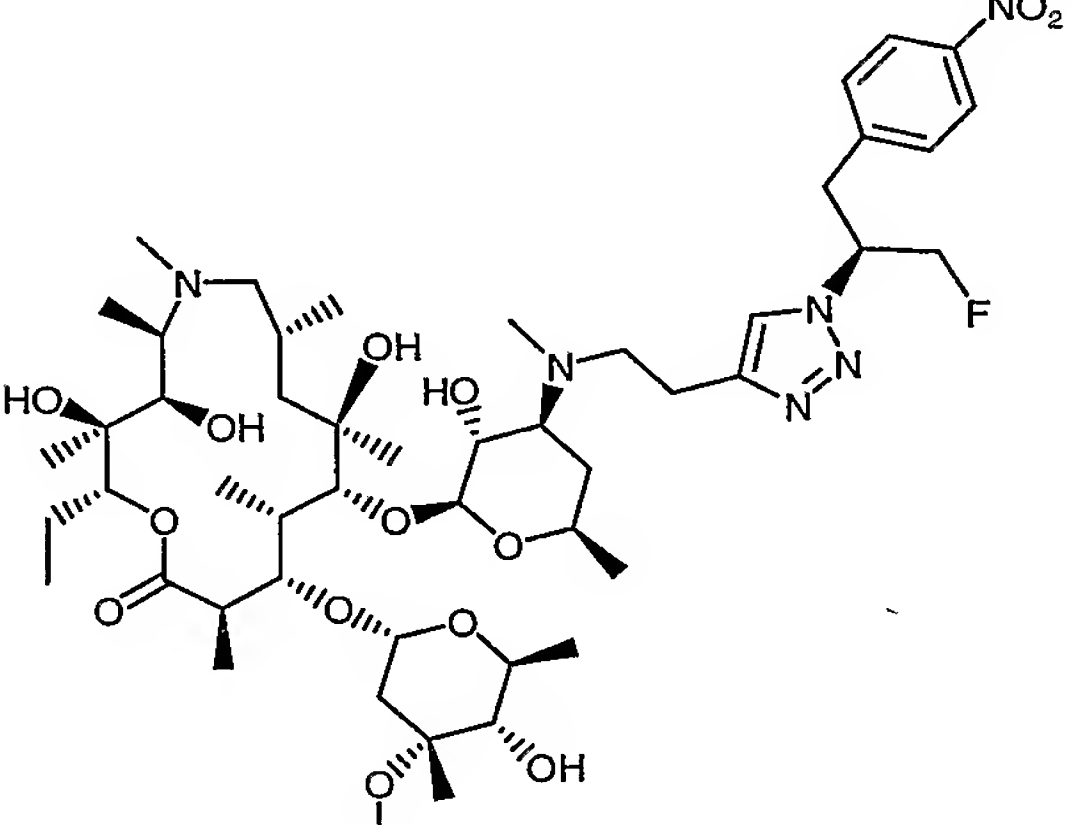
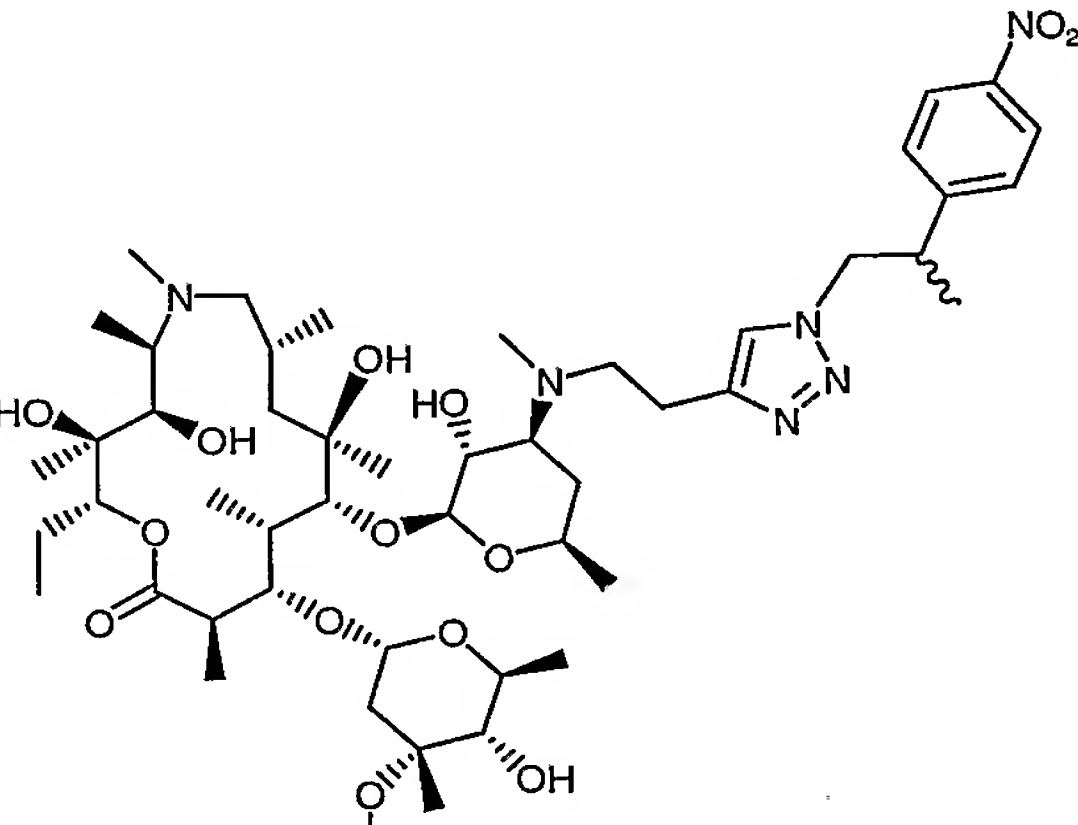
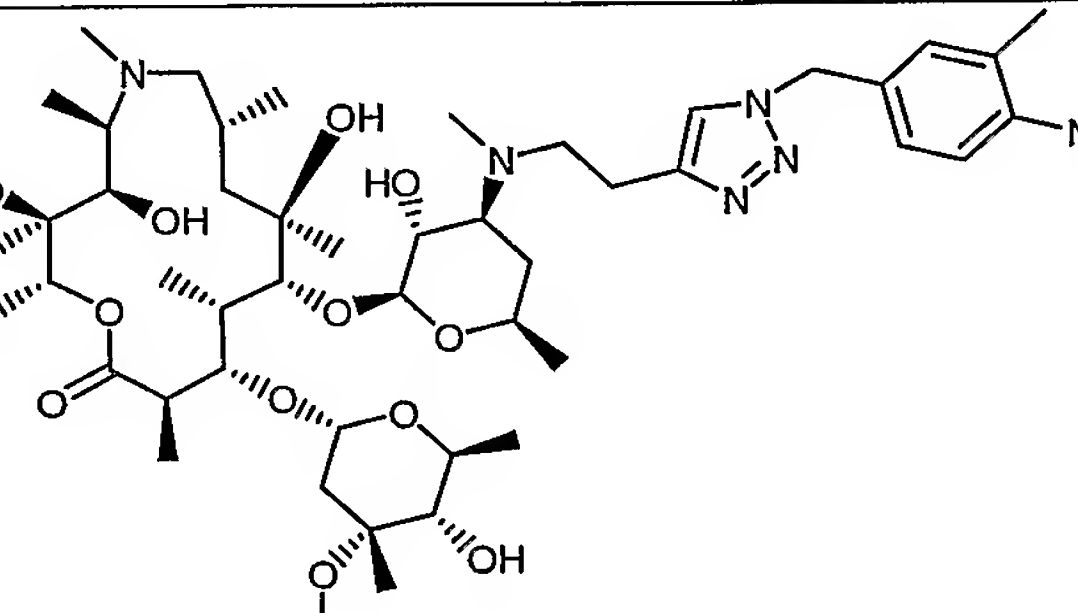
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164	 <p>Chemical structure 164: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring, a fluorophenyl group, and a sulfonamide group.</p>
165	 <p>Chemical structure 165: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring and a phenyl group with a hydroxyl group.</p>
166	 <p>Chemical structure 166: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring and a phenyl group with a carbonyl group.</p>
167	 <p>Chemical structure 167: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring and a phenyl group with a hydroxyl group.</p>

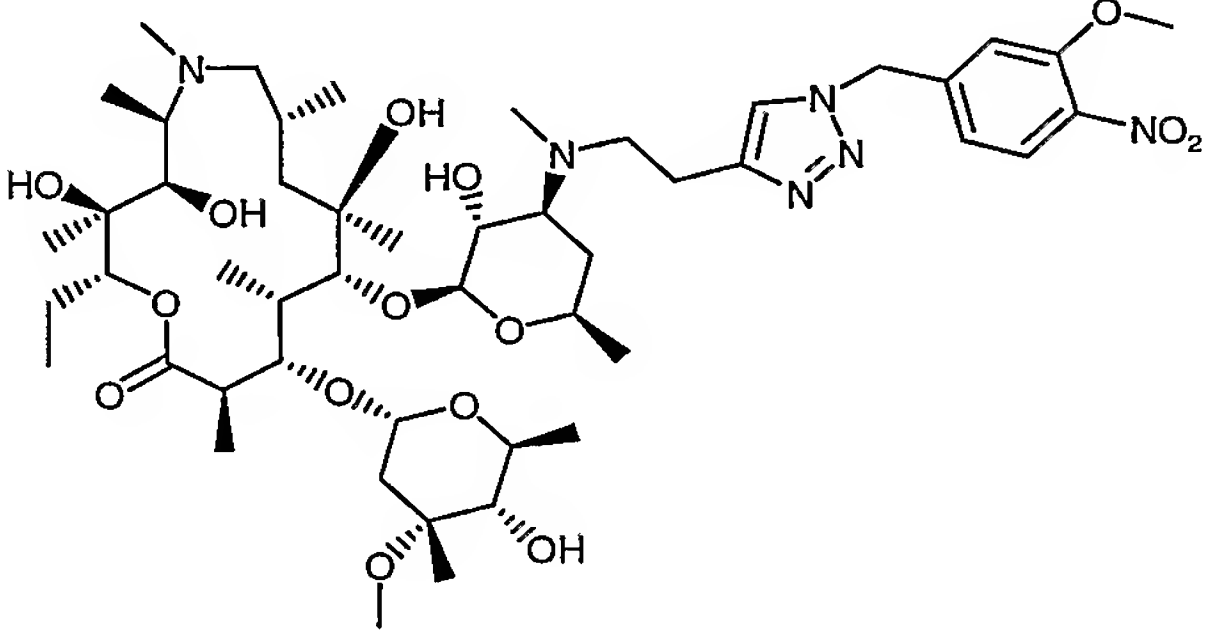
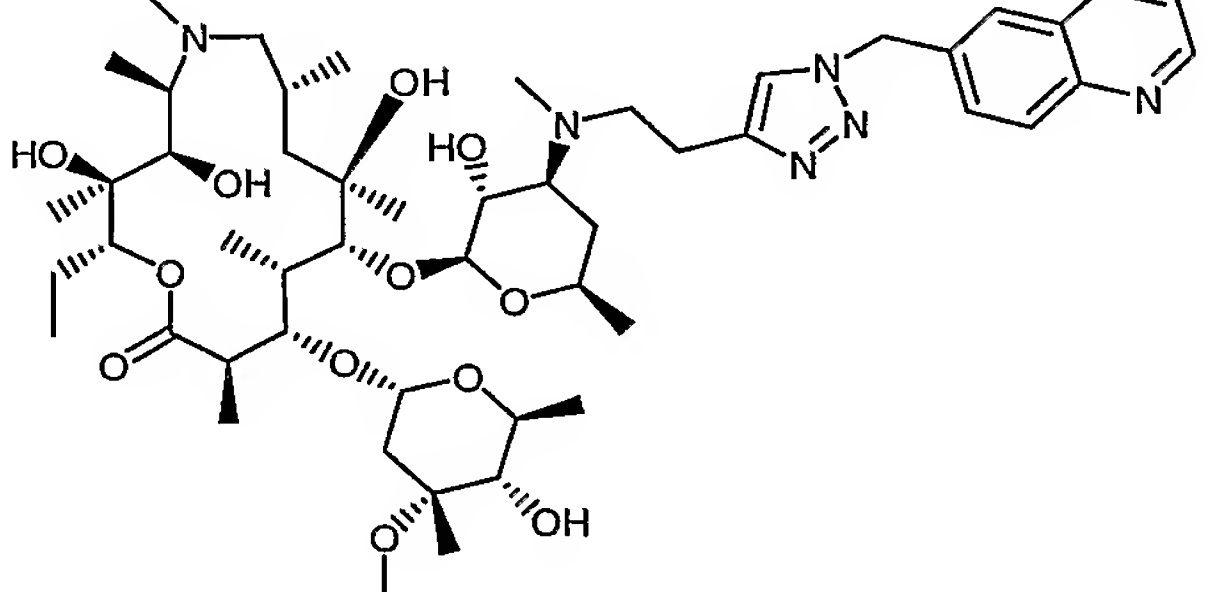
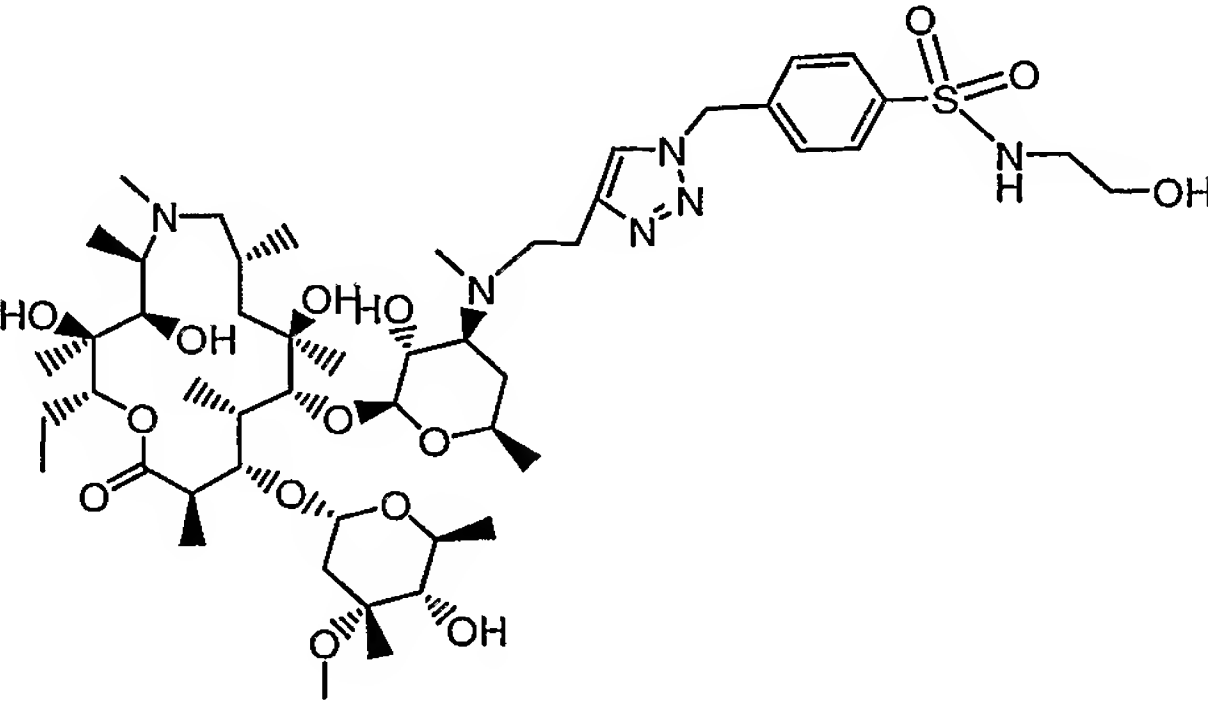
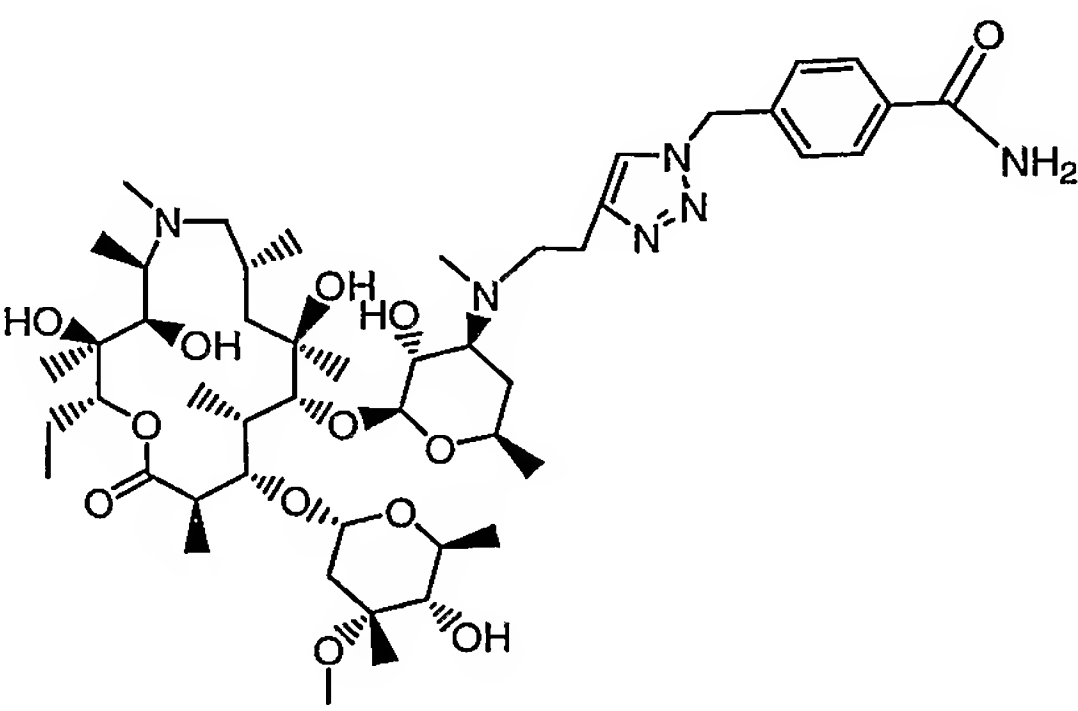
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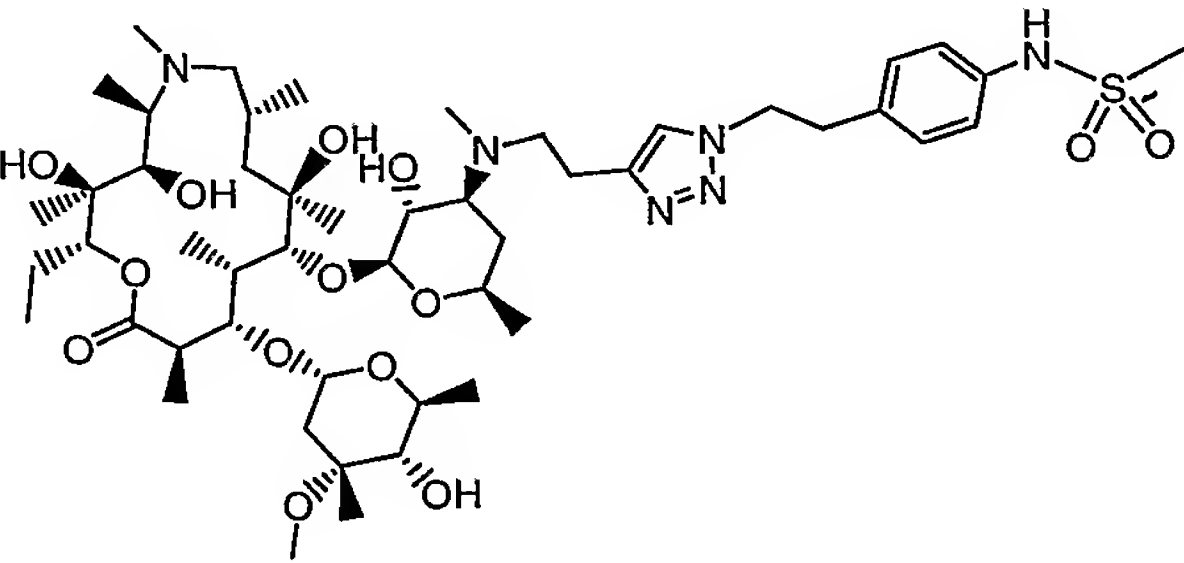
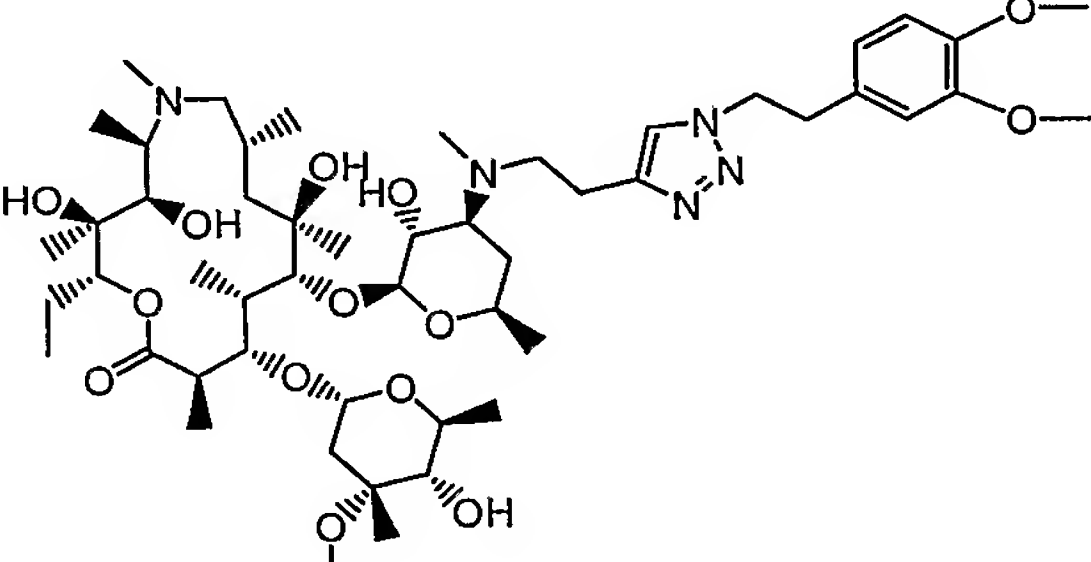
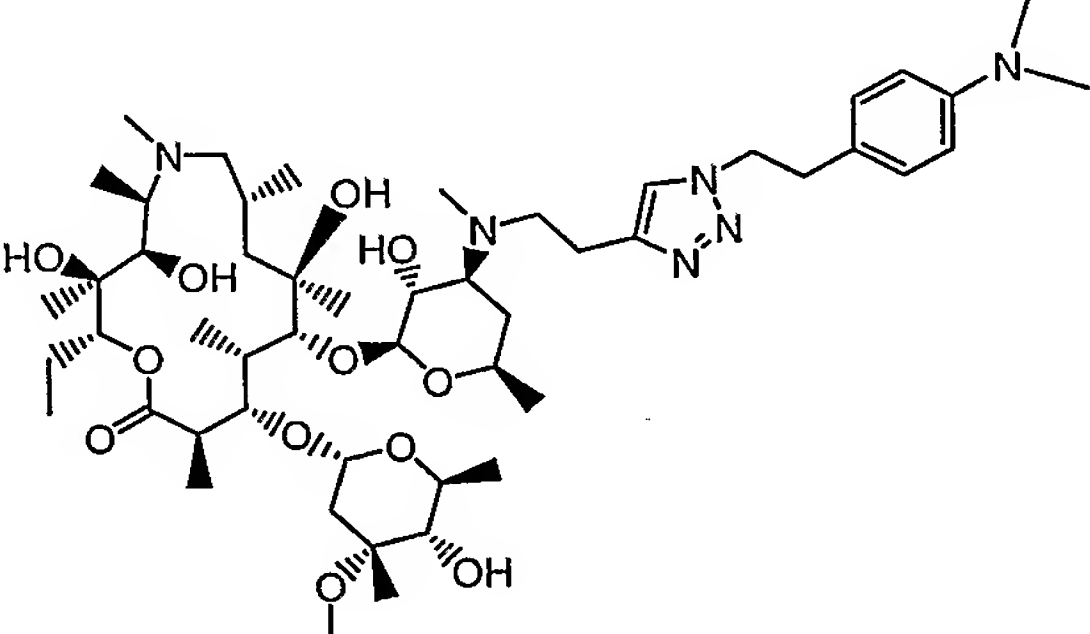
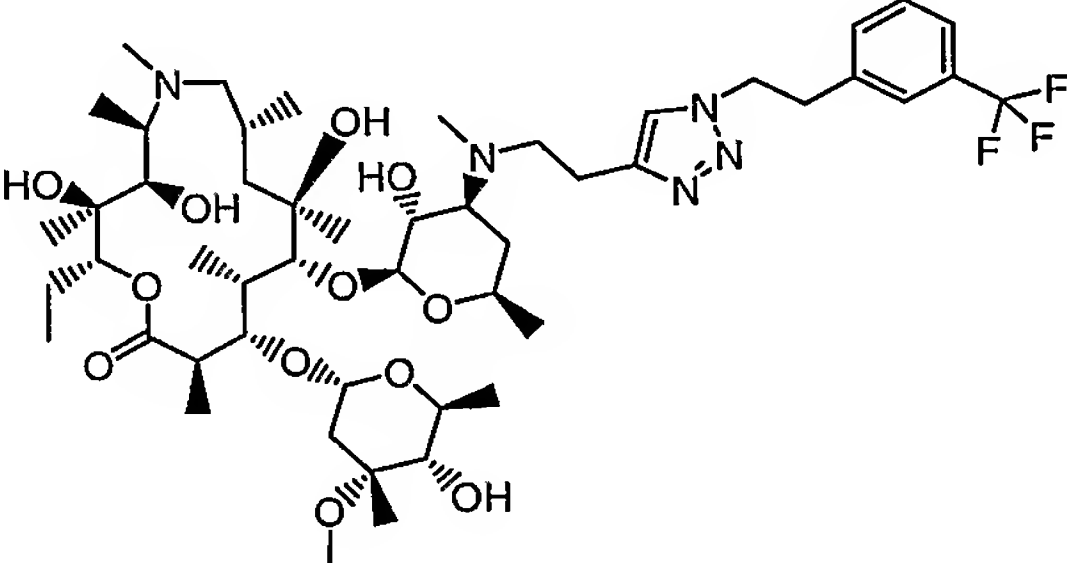
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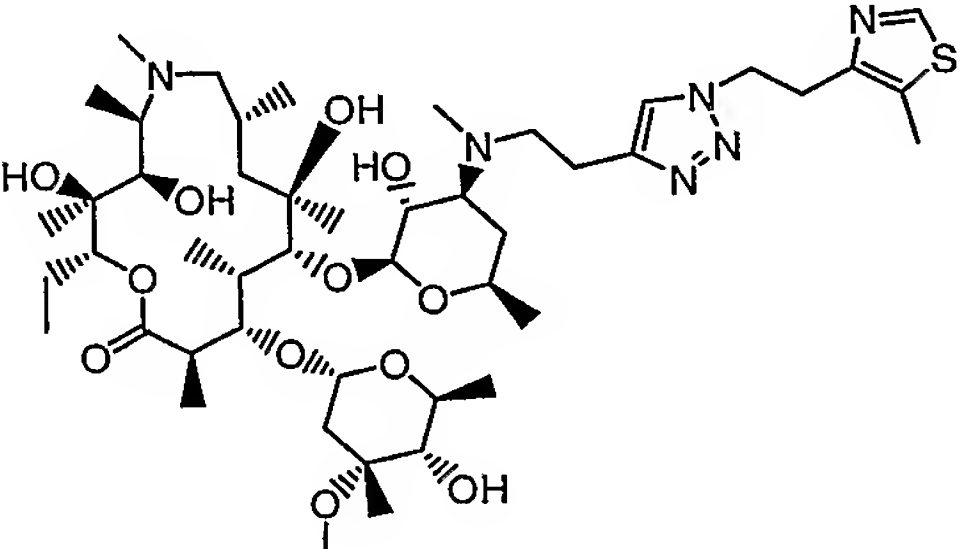
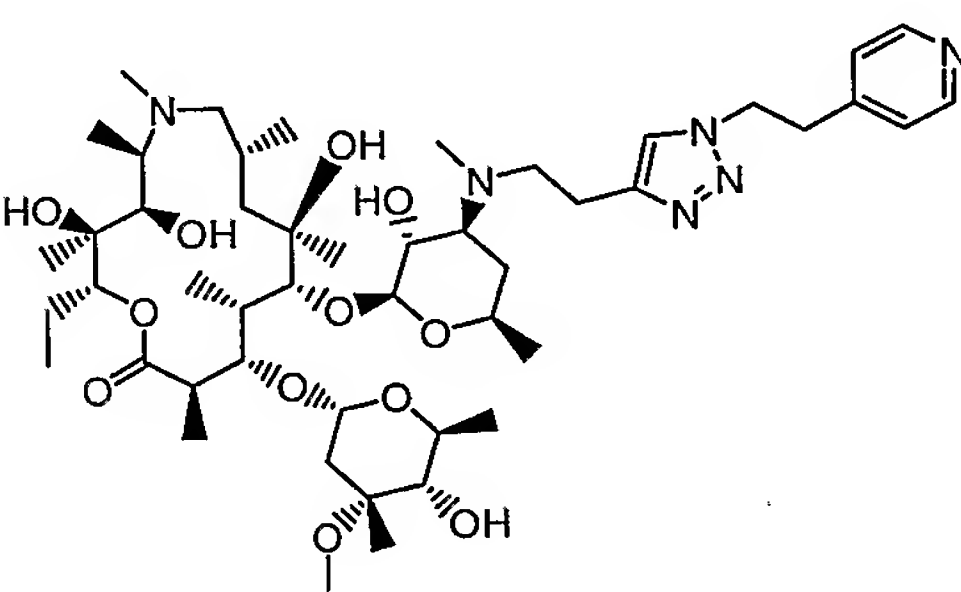
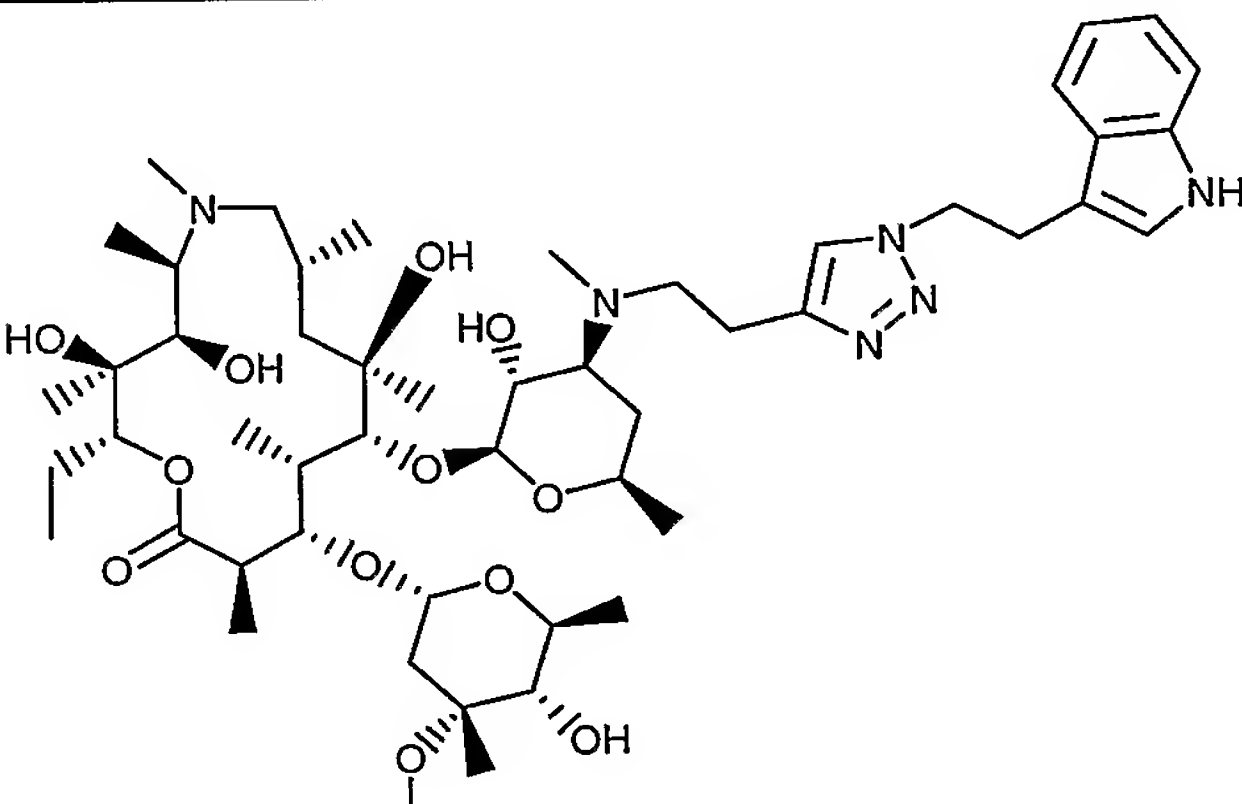
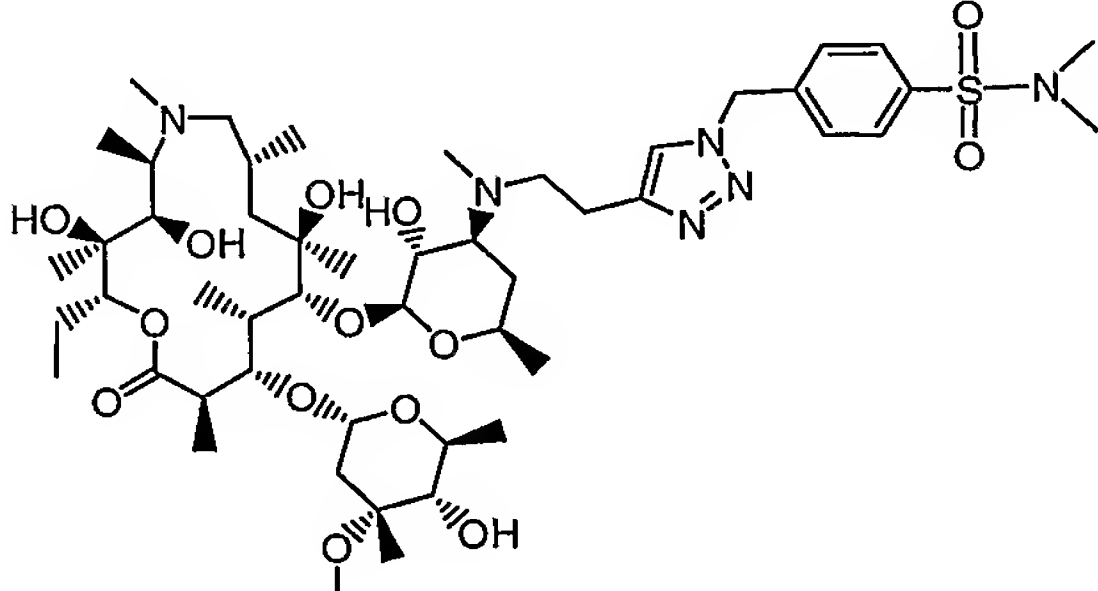
171	 <p>Chemical structure 171 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a nitro-substituted phenyl ring attached via a triazole linker. The structure includes a central bicyclic system with several hydroxyl groups and a nitro-substituted phenyl ring attached via a triazole linker.</p>
172	 <p>Chemical structure 172 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a nitro-substituted phenyl ring attached via a triazole linker. The structure includes a central bicyclic system with several hydroxyl groups and a nitro-substituted phenyl ring attached via a triazole linker.</p>
173	 <p>Chemical structure 173 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a nitro-substituted phenyl ring attached via a triazole linker. The structure includes a central bicyclic system with several hydroxyl groups and a nitro-substituted phenyl ring attached via a triazole linker.</p>

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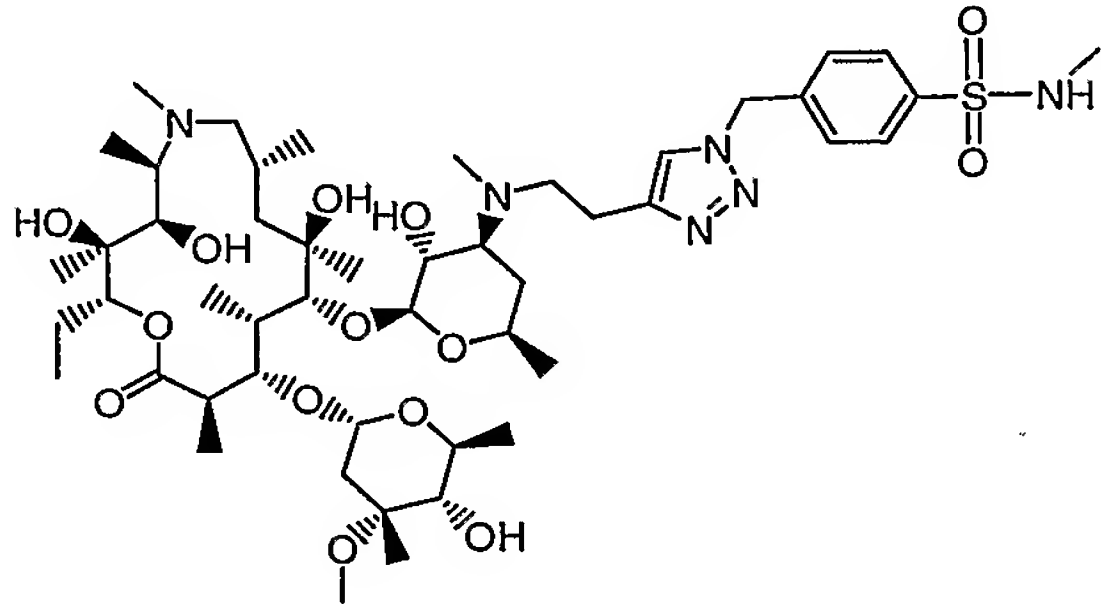
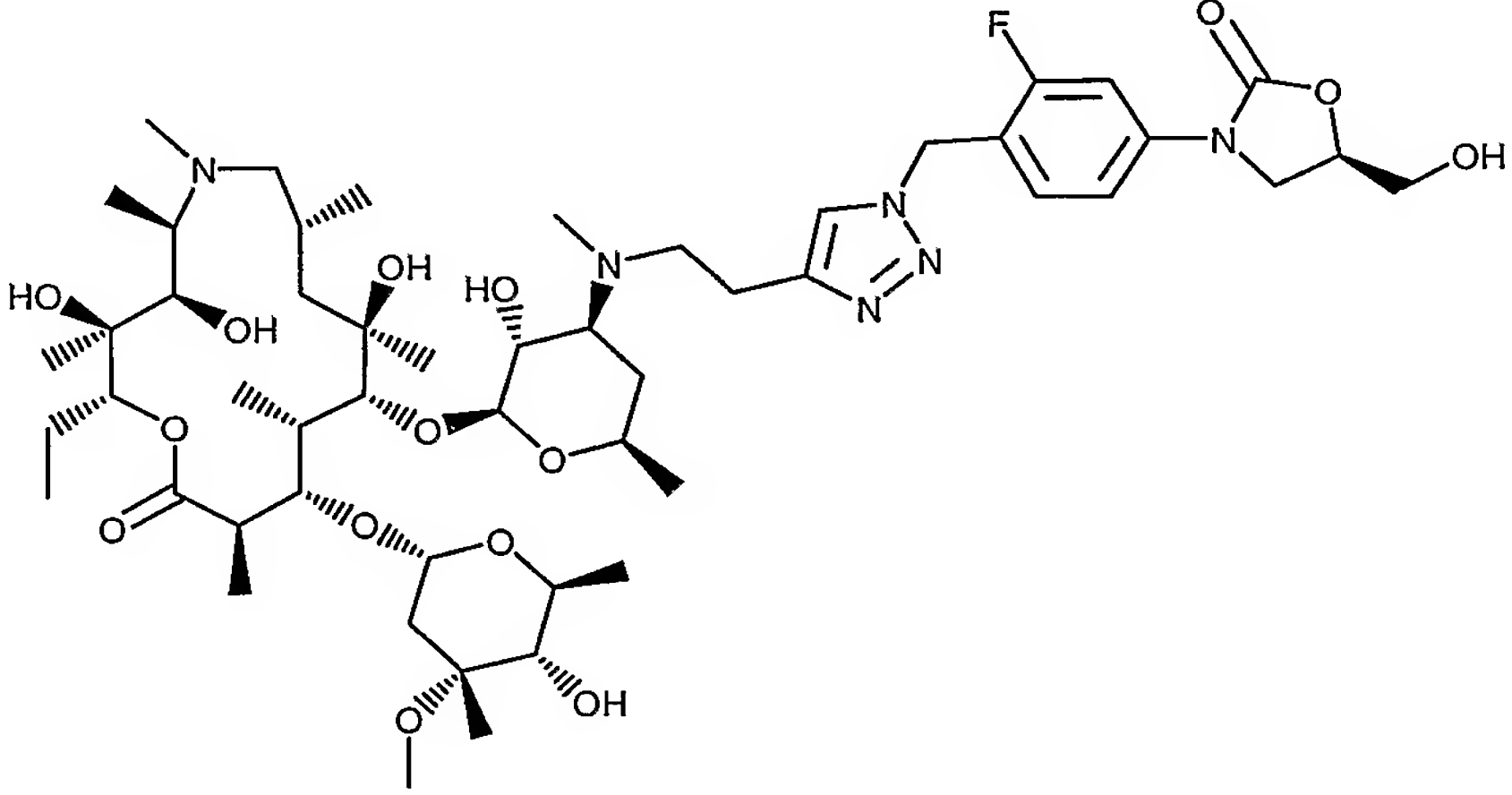
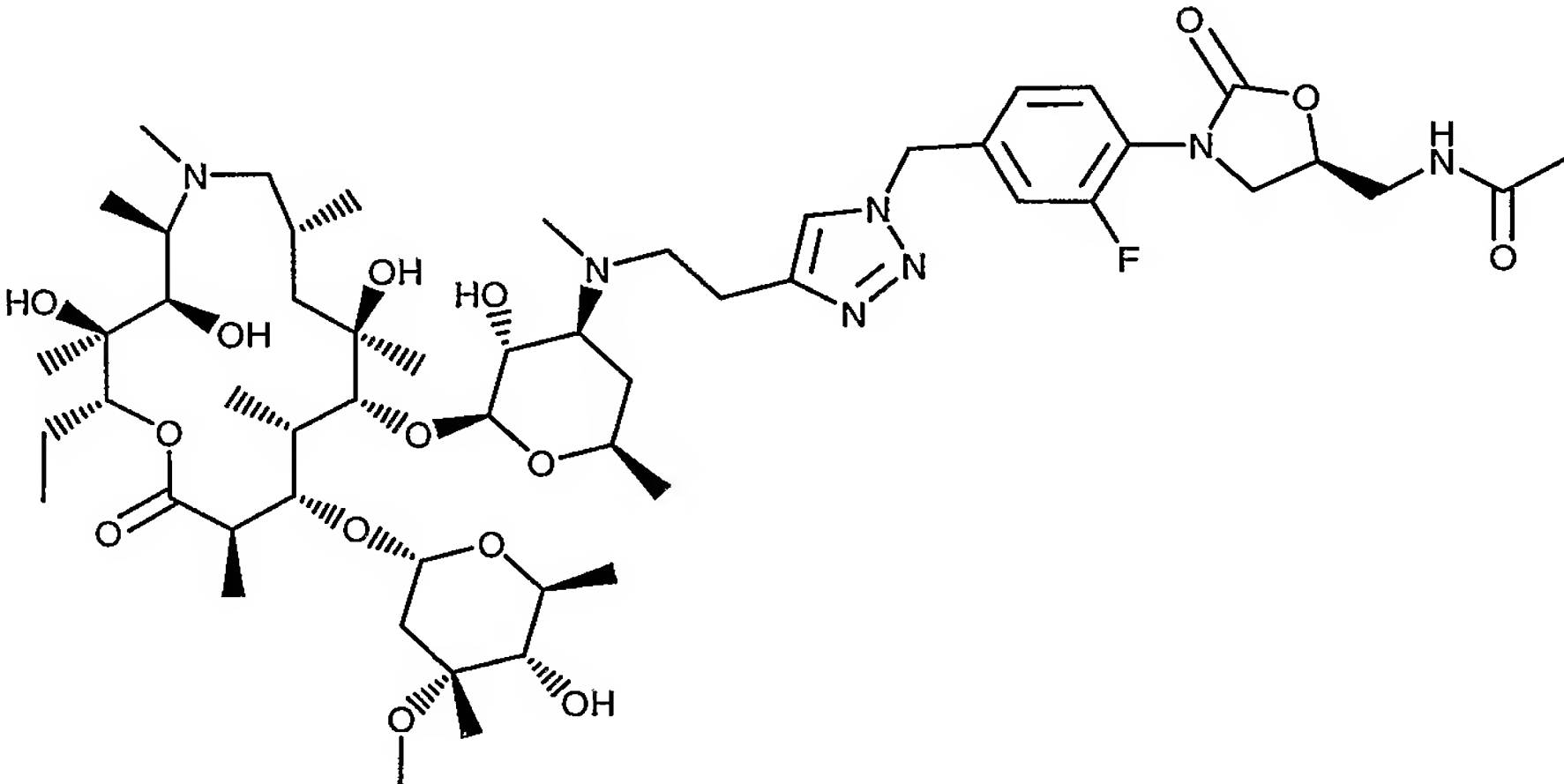
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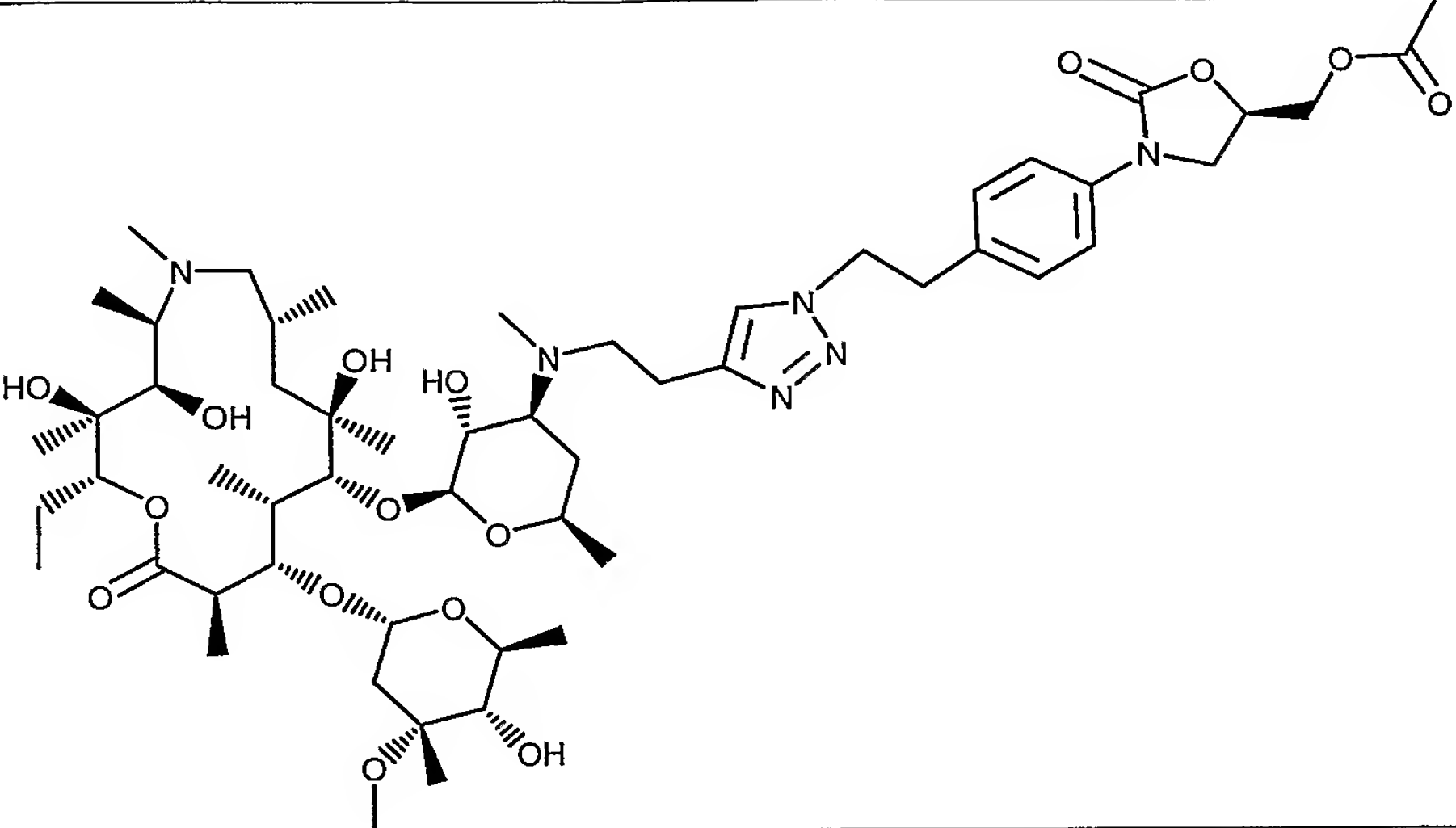
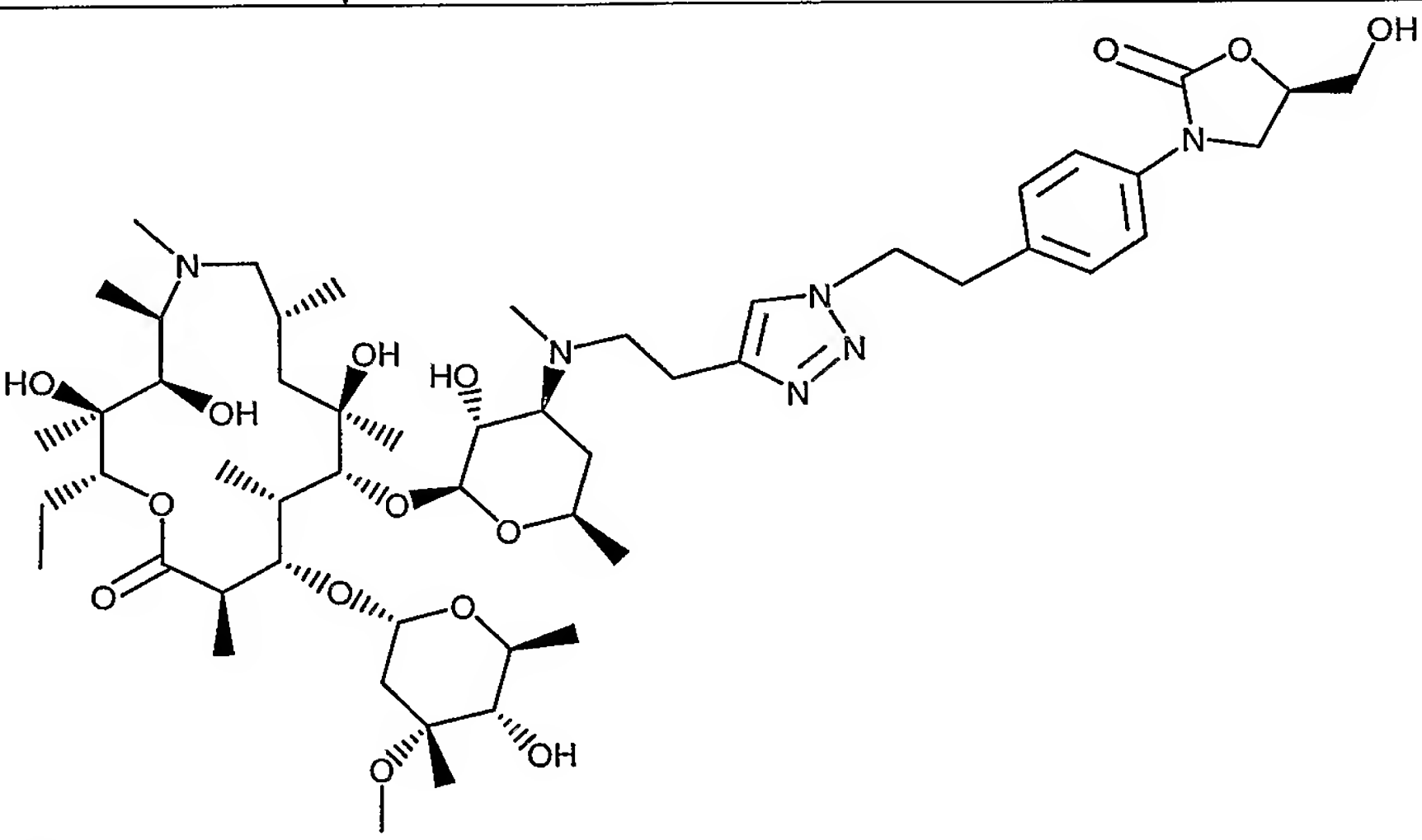
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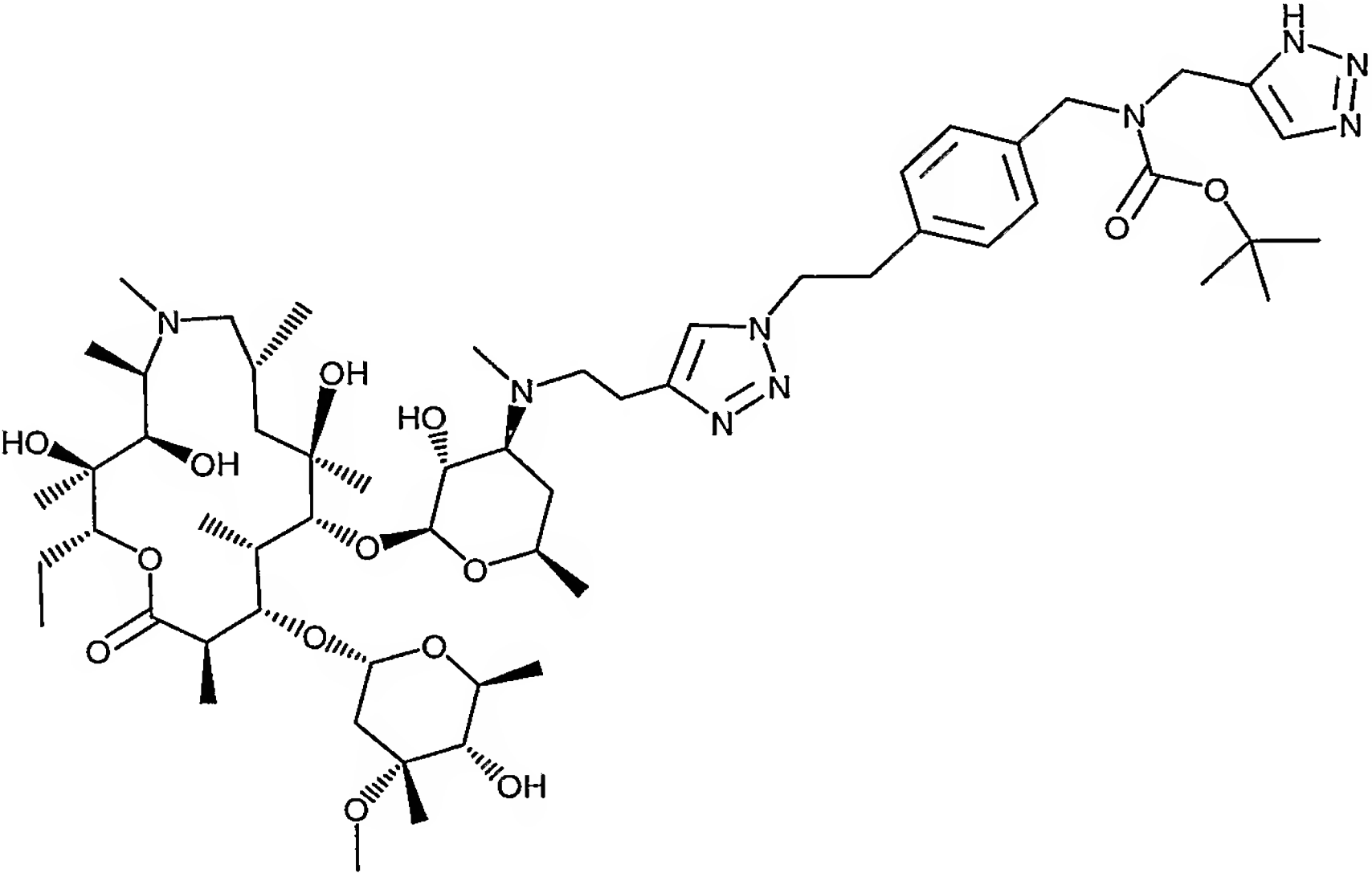
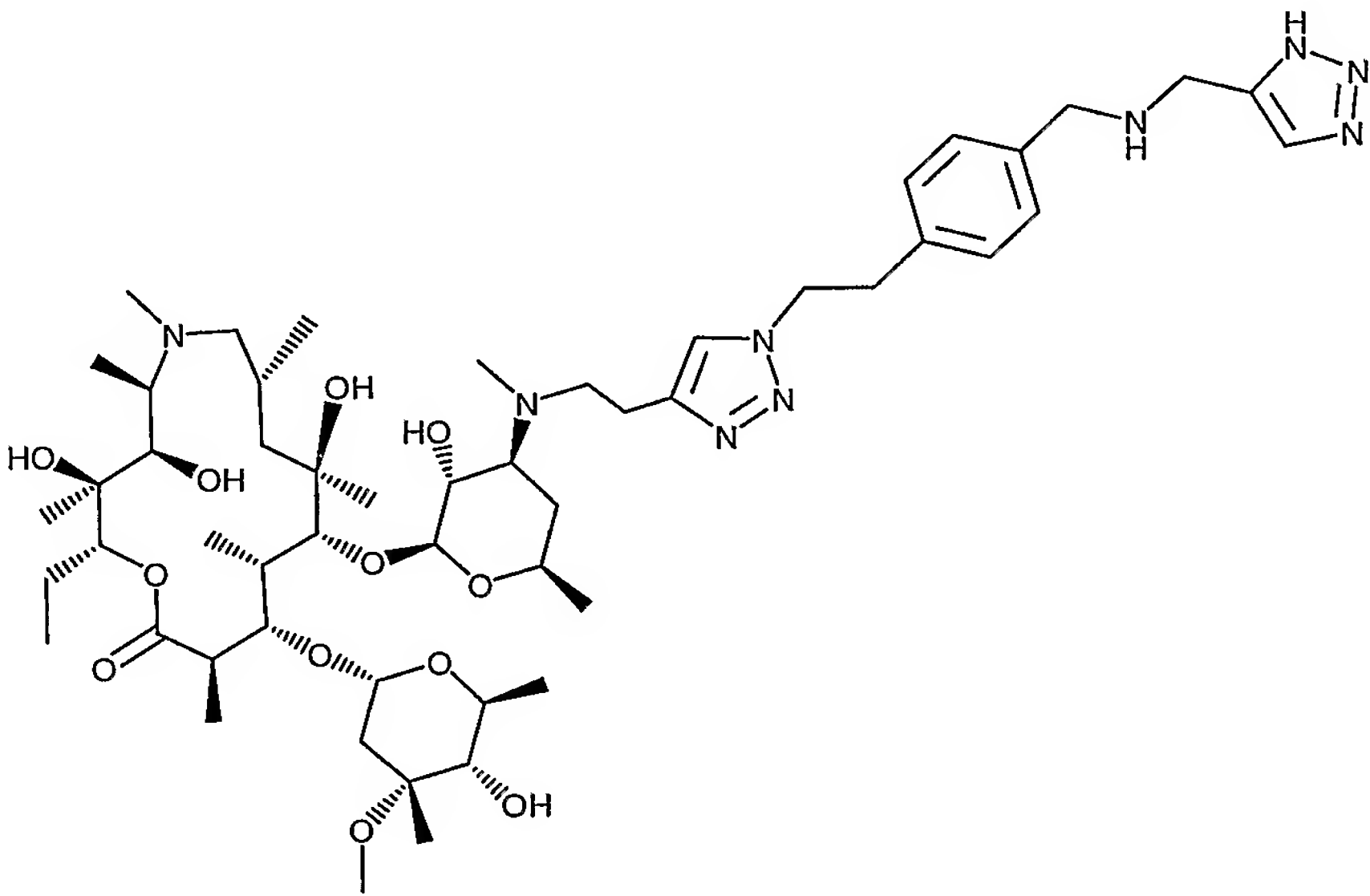
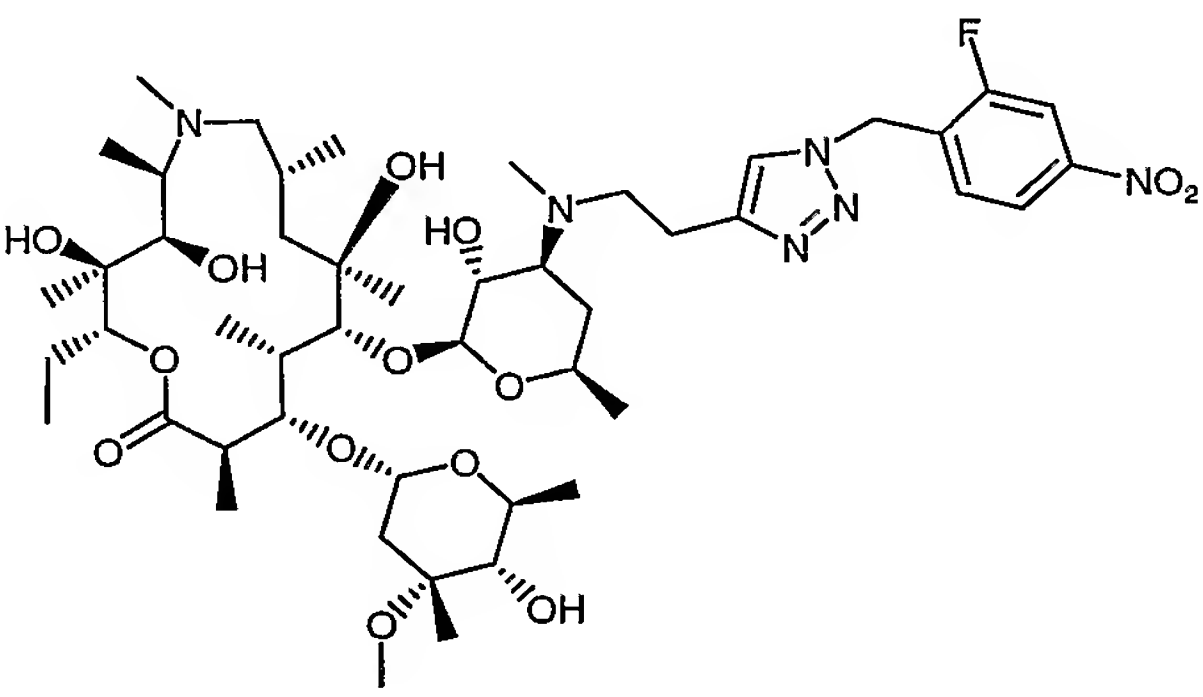
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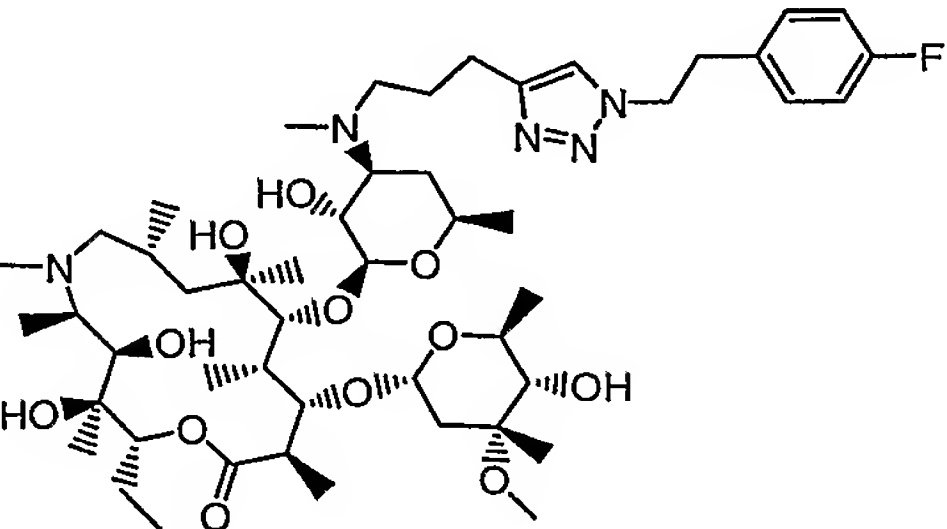
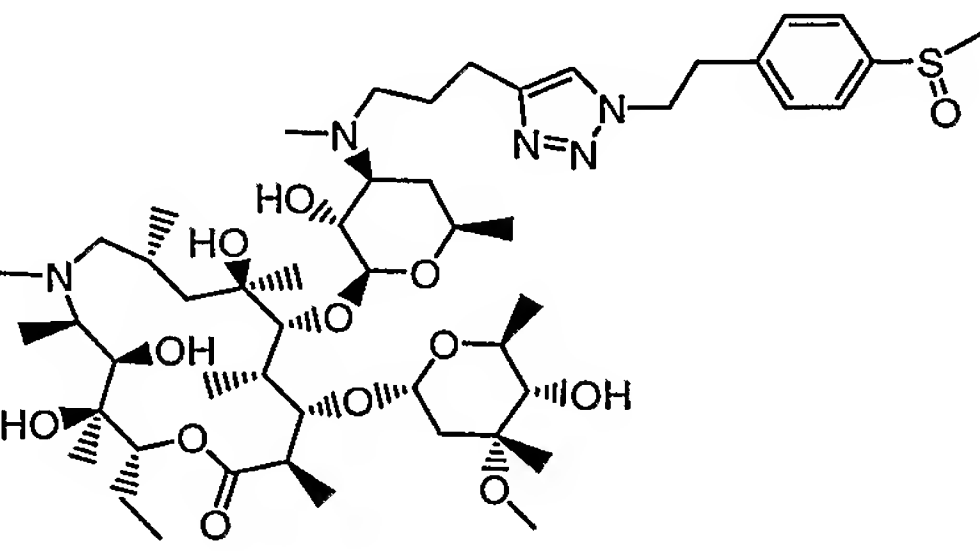
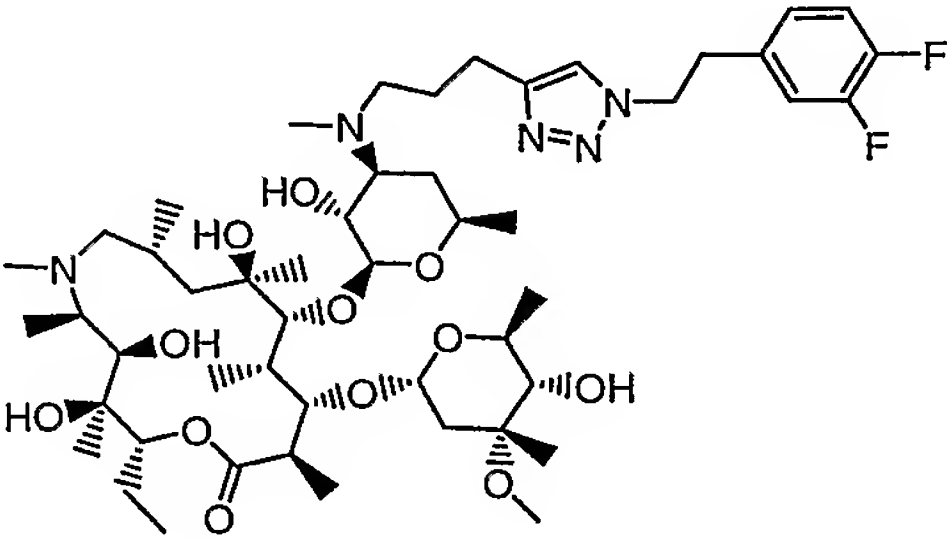
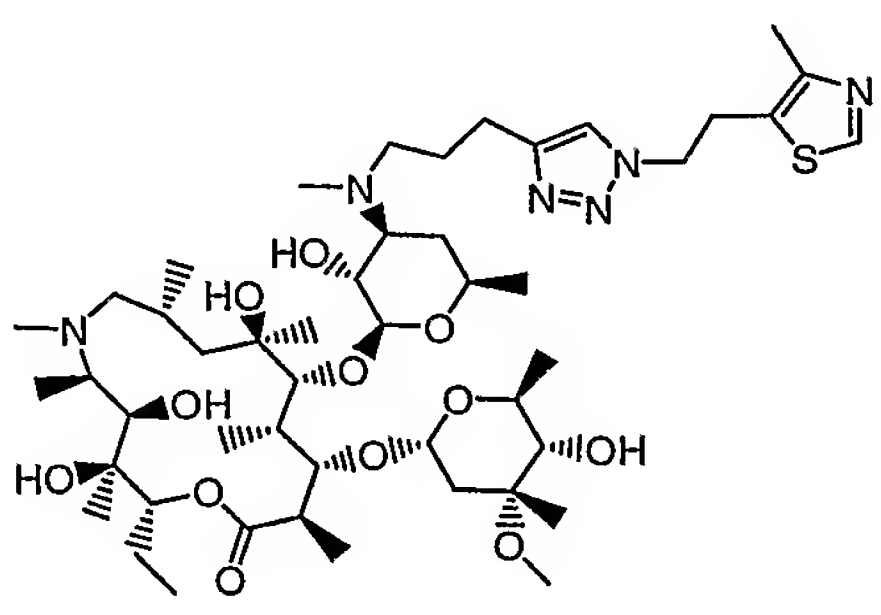
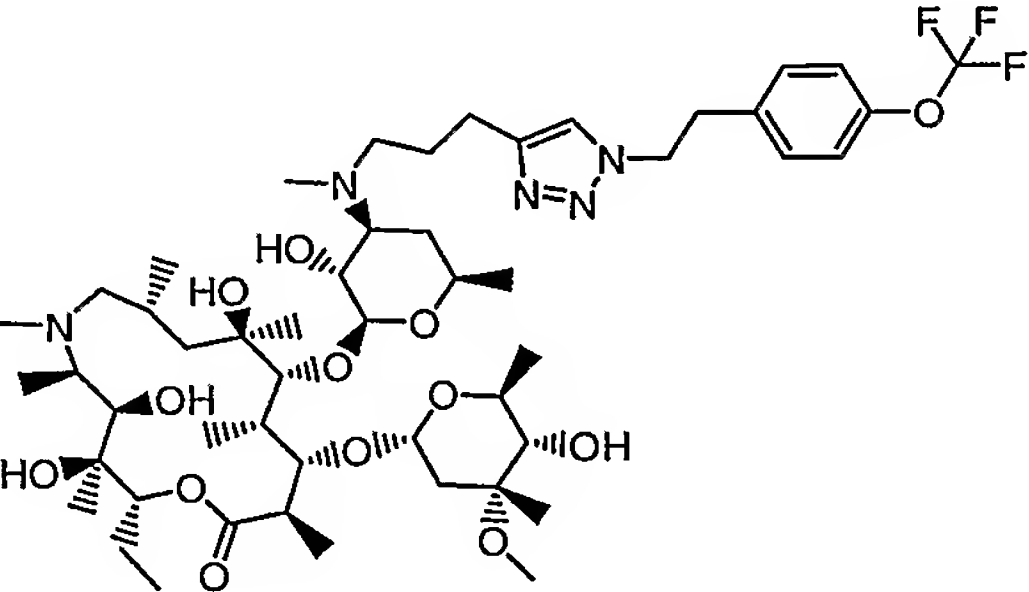
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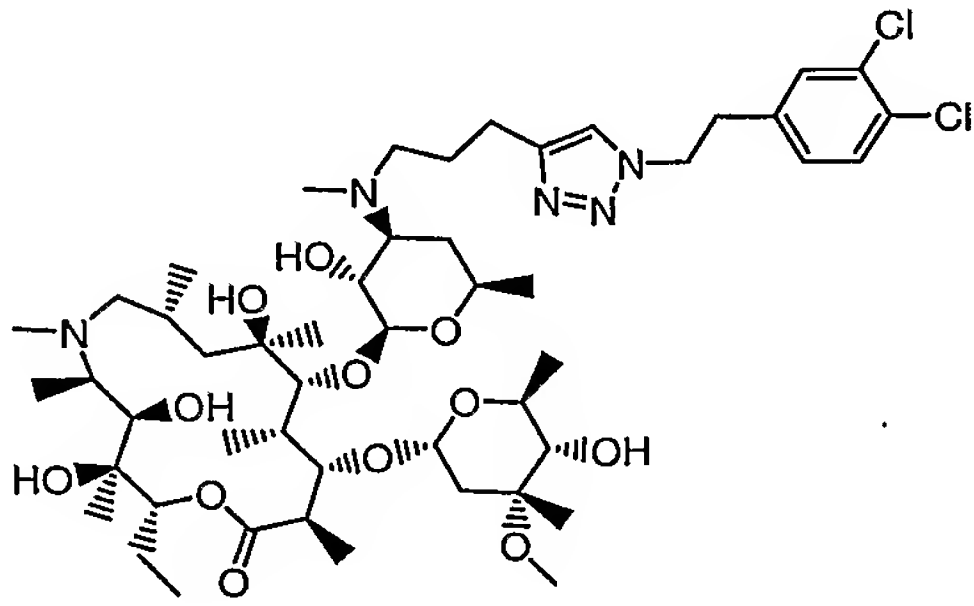
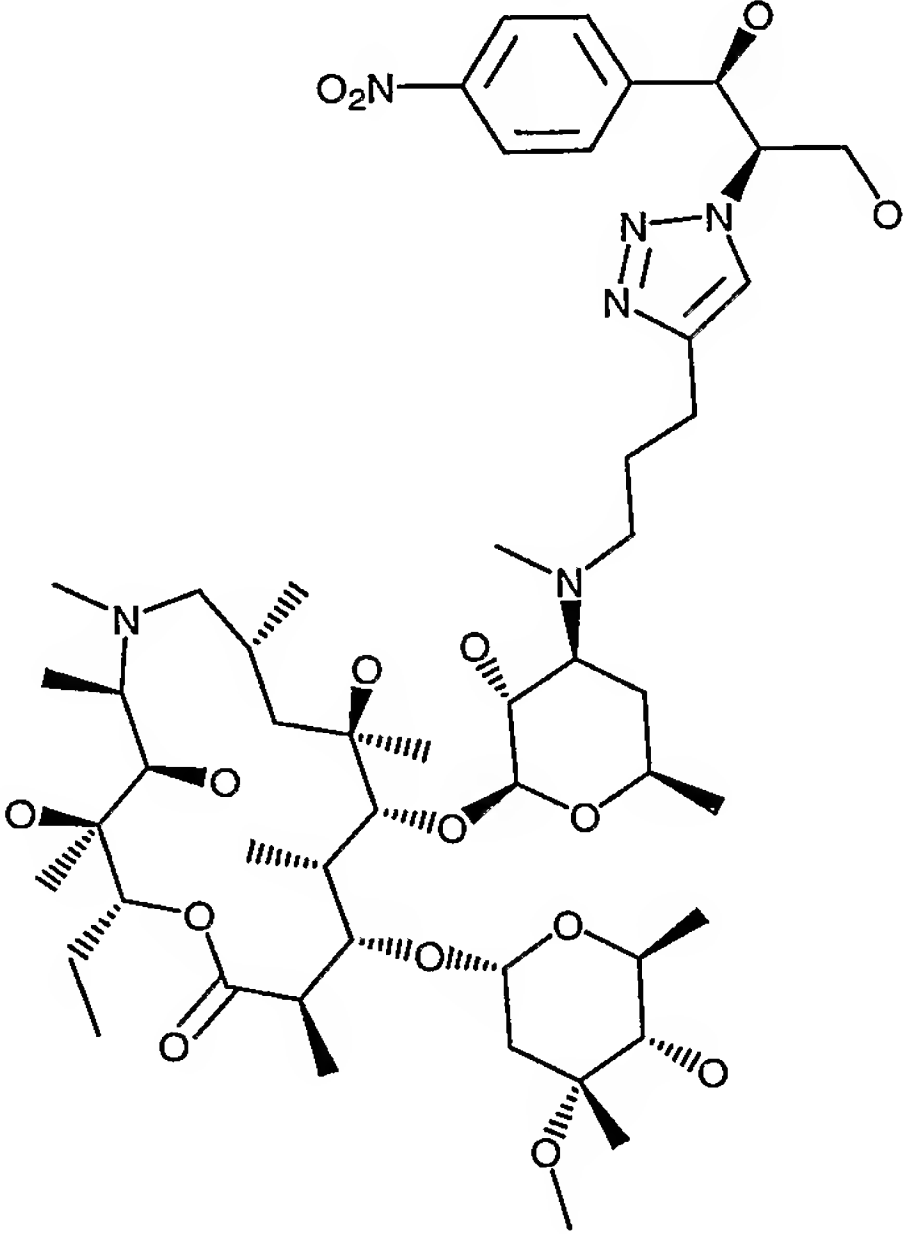
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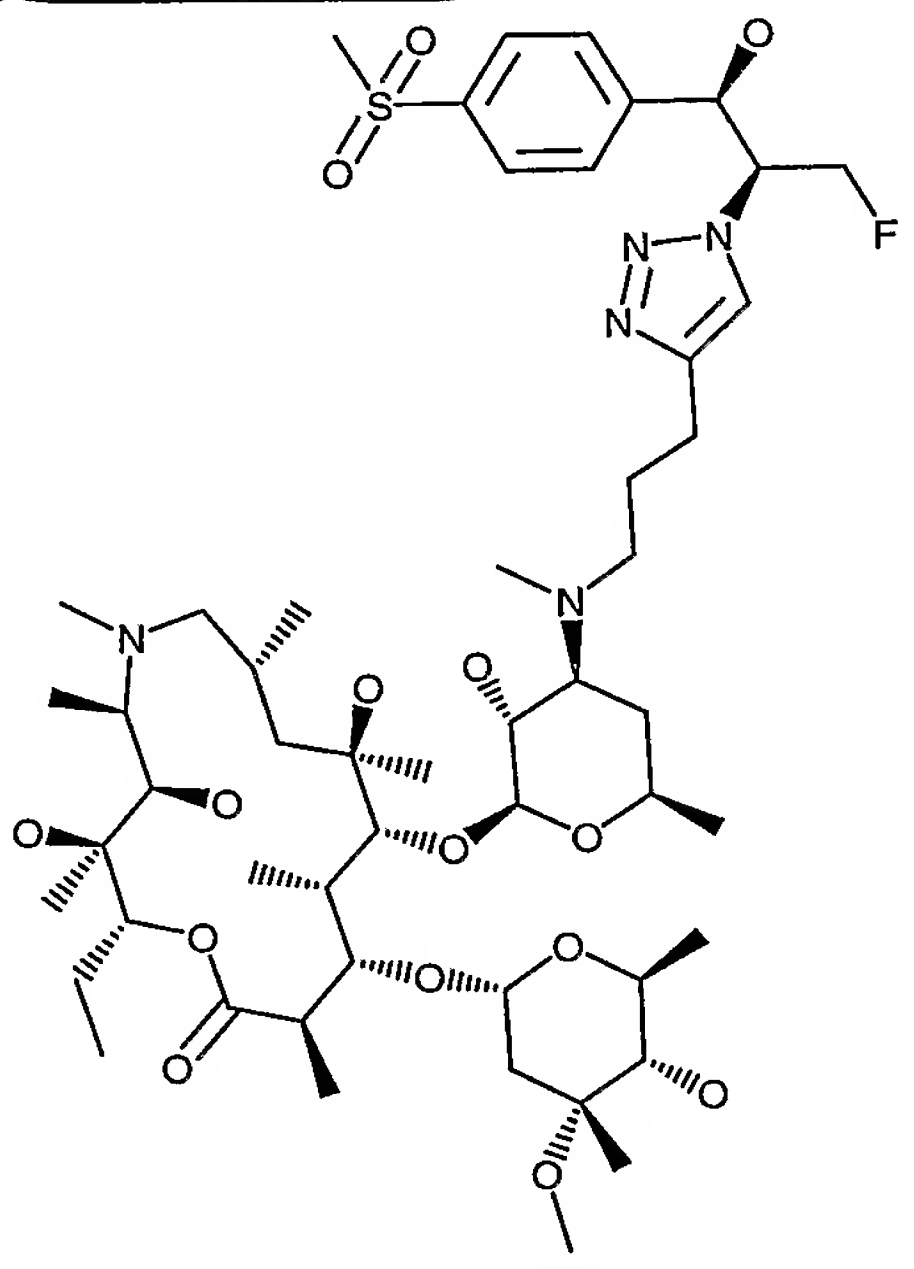
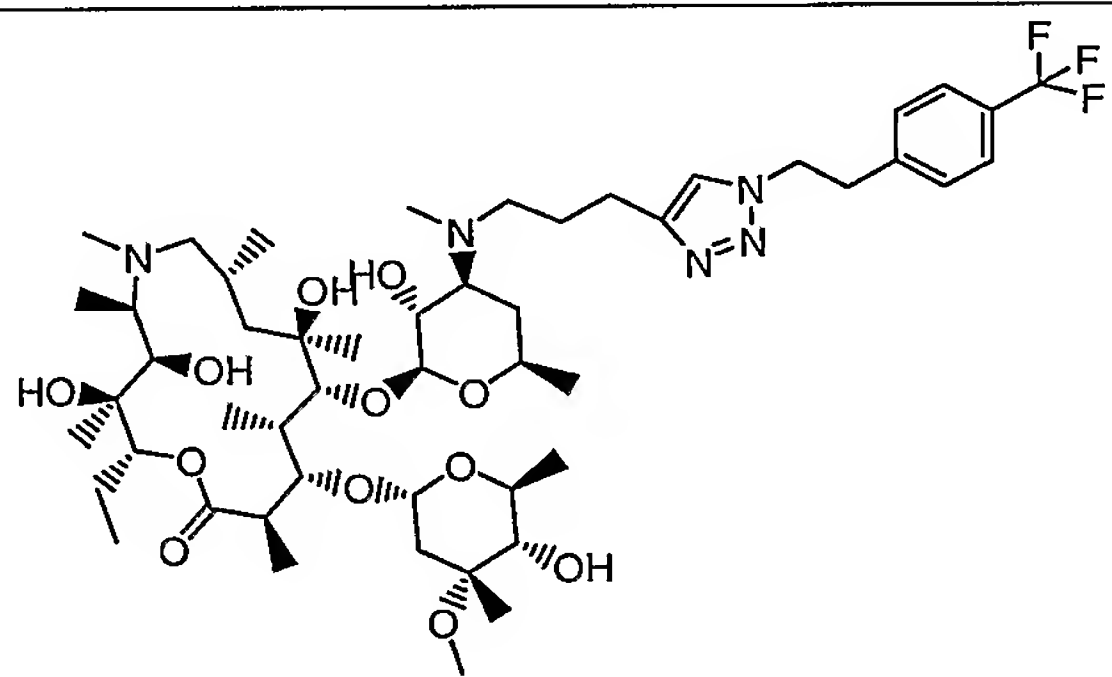
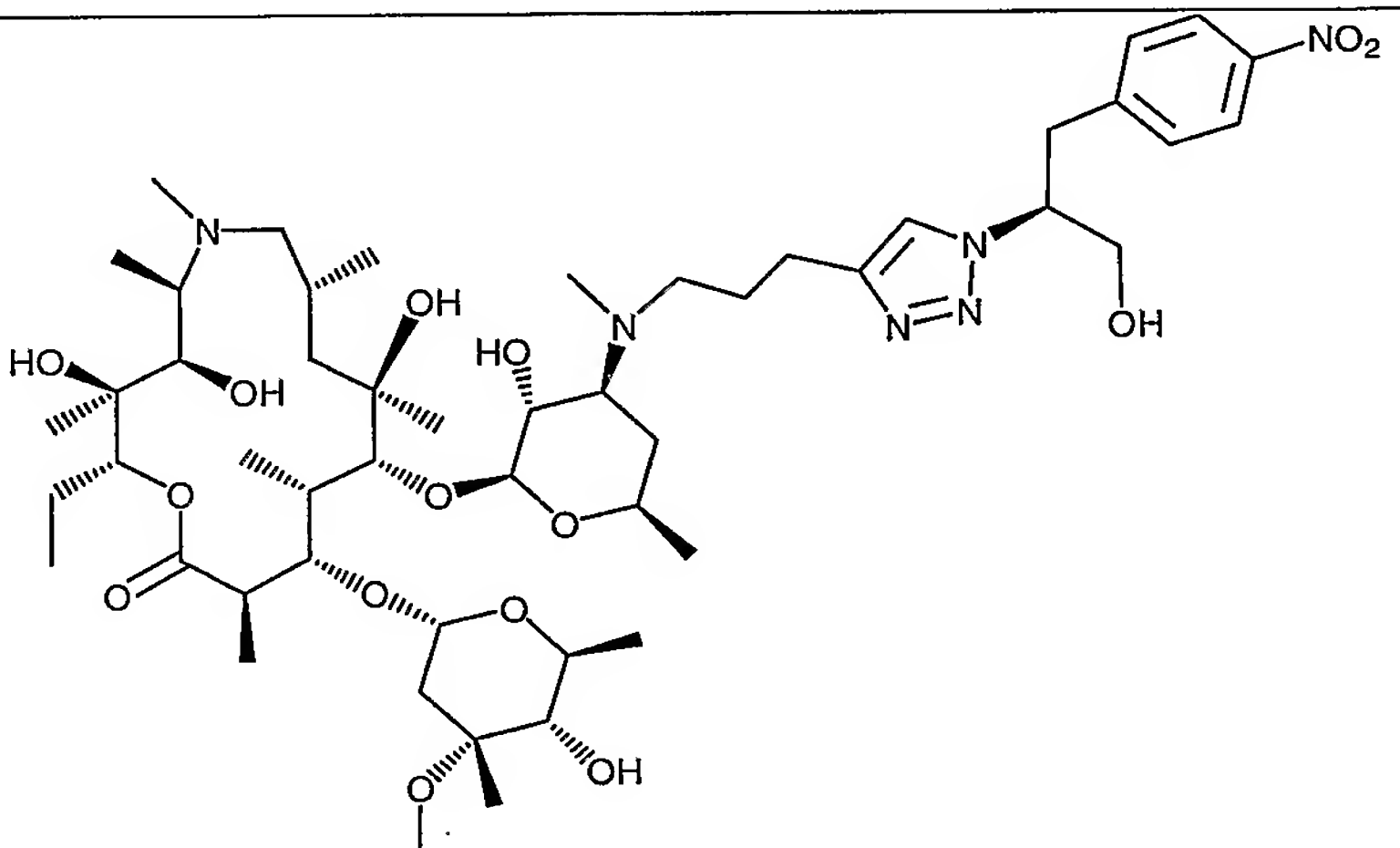
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195	 <p>Chemical structure of compound 195, a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring, a phenyl group, and a tert-butyl ester.</p>
196	 <p>Chemical structure of compound 196, a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring, a phenyl group, and a primary amine.</p>
197	 <p>Chemical structure of compound 197, a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring, a phenyl group, and a nitro group.</p>

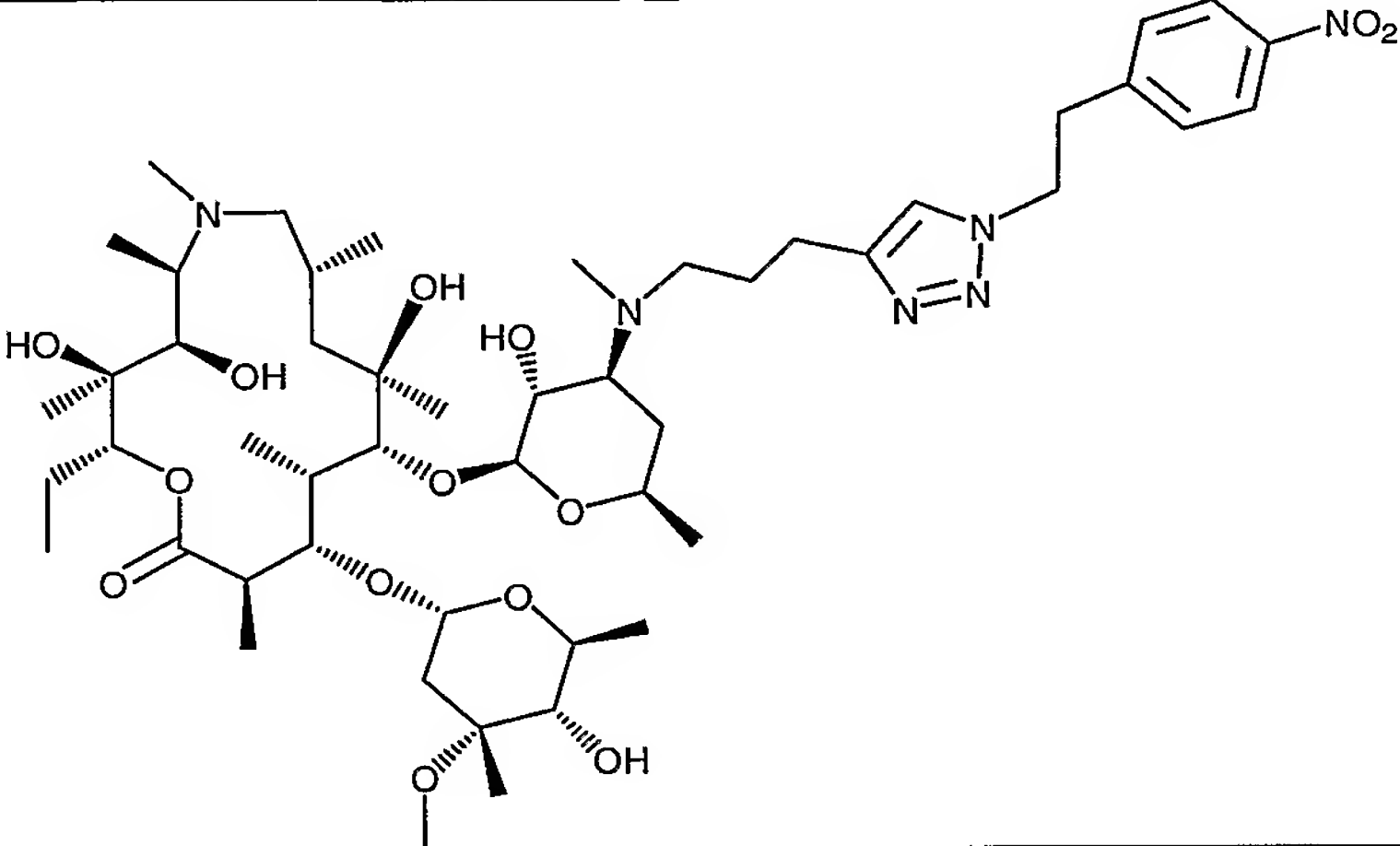
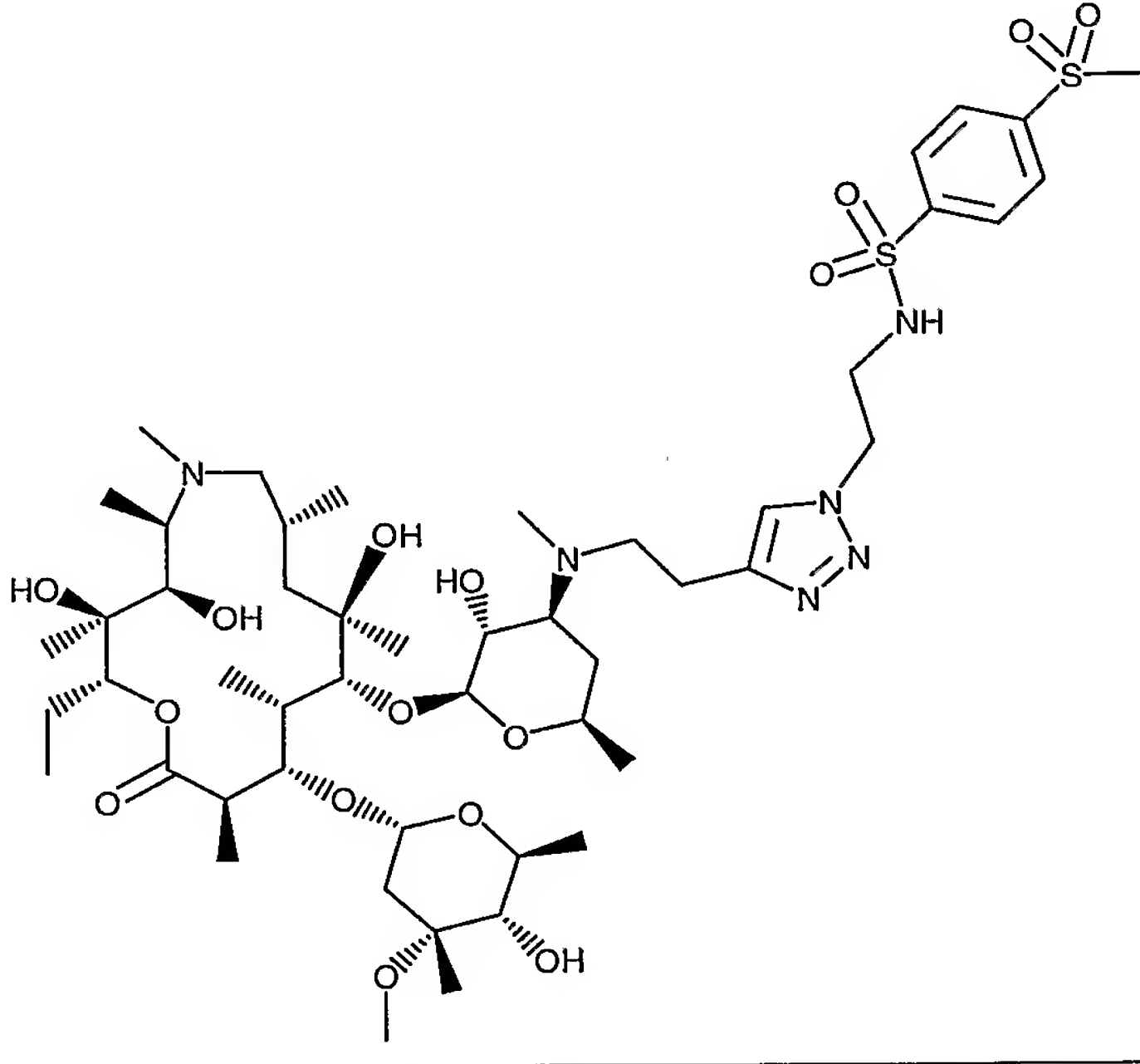
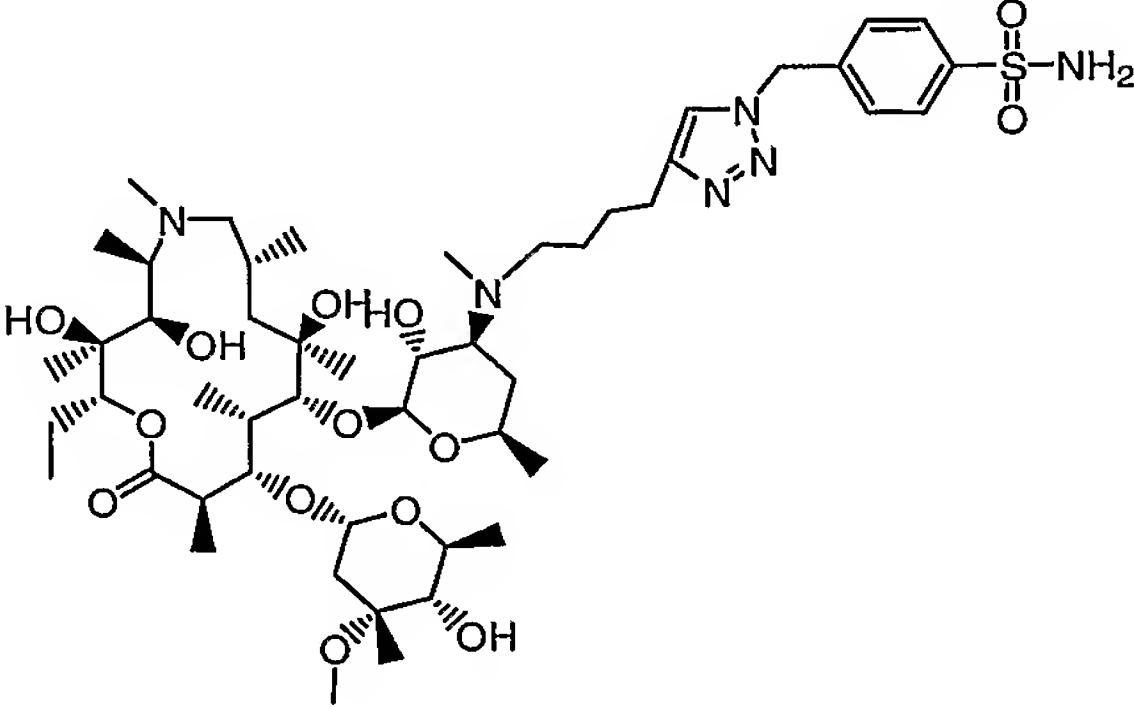
198	 <p>Chemical structure 198: A complex polycyclic molecule, likely a steroid or similar, featuring multiple hydroxyl groups and a side chain ending in a 4-fluorophenyl group.</p>
199	 <p>Chemical structure 199: A complex polycyclic molecule, similar to 198, but with a side chain ending in a 4-(methylsulfonyl)phenyl group.</p>
200	 <p>Chemical structure 200: A complex polycyclic molecule, similar to 198, but with a side chain ending in a 3,5-difluorophenyl group.</p>
201	 <p>Chemical structure 201: A complex polycyclic molecule, similar to 198, but with a side chain ending in a 4-methylthienyl group.</p>
202	 <p>Chemical structure 202: A complex polycyclic molecule, similar to 198, but with a side chain ending in a 4-(trifluoromethoxy)phenyl group.</p>

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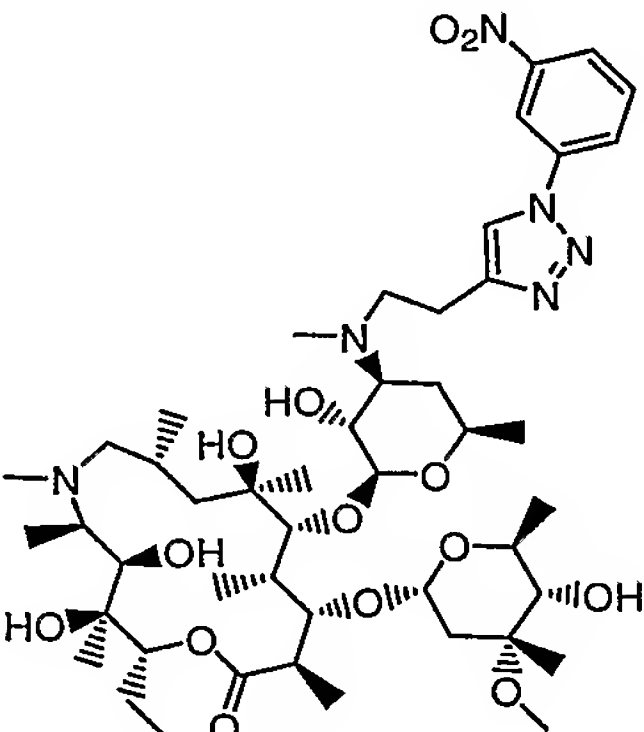
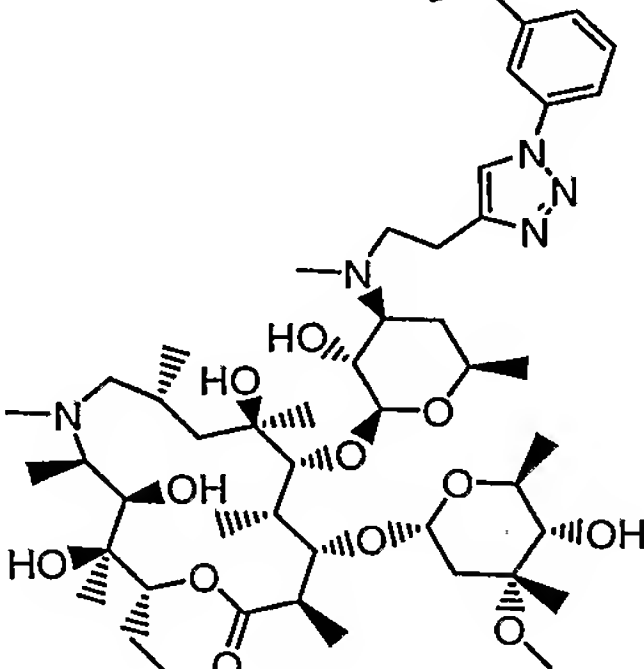
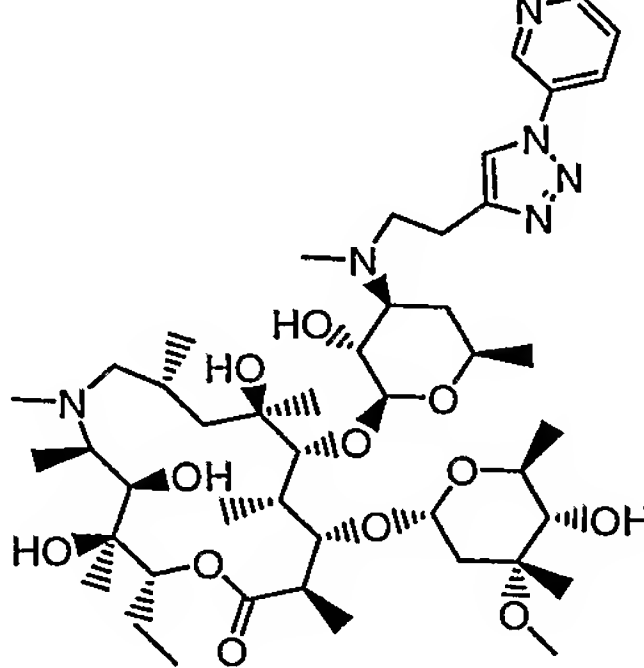
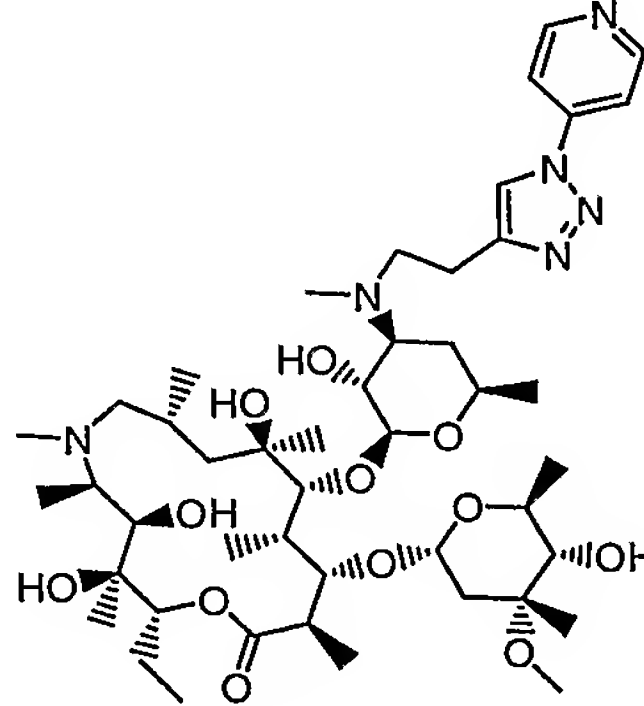
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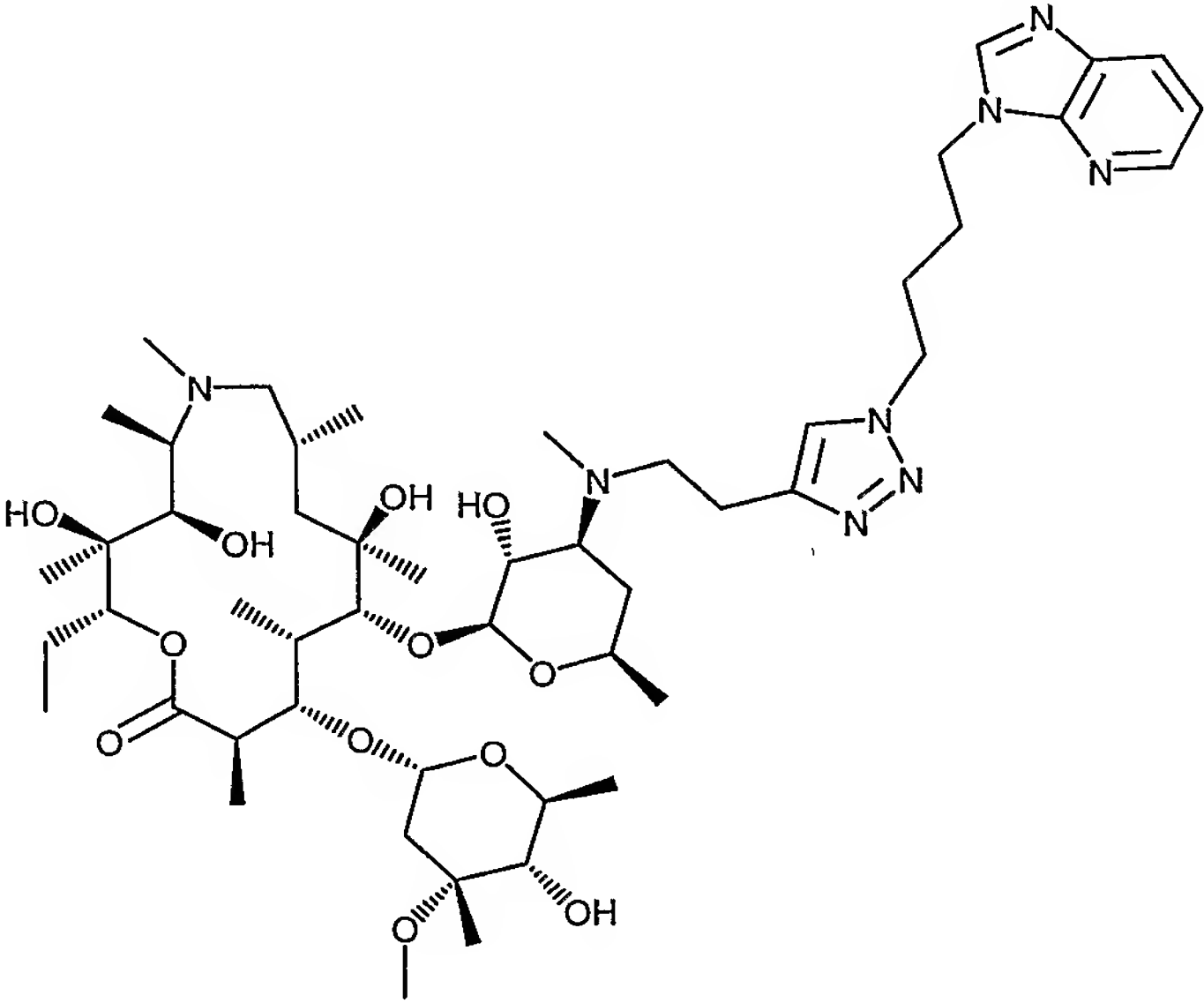
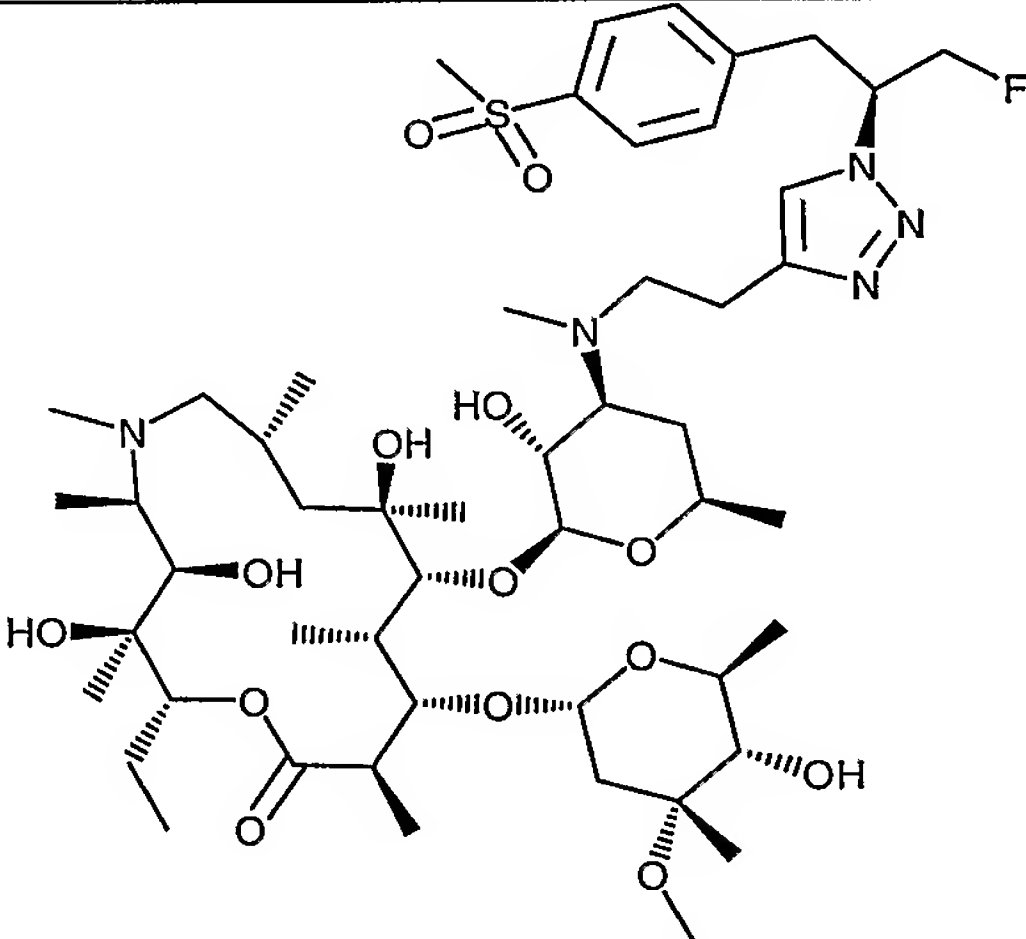
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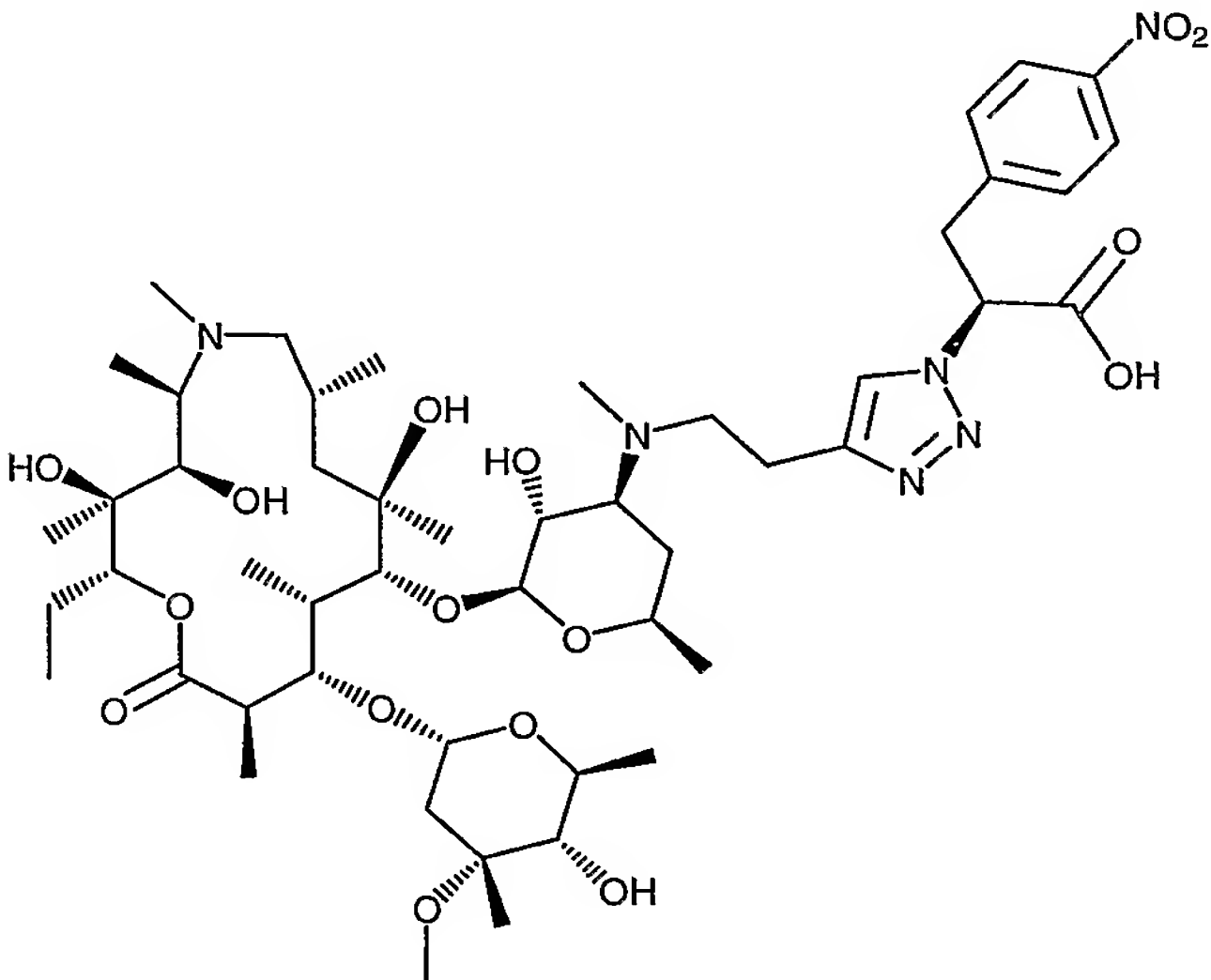
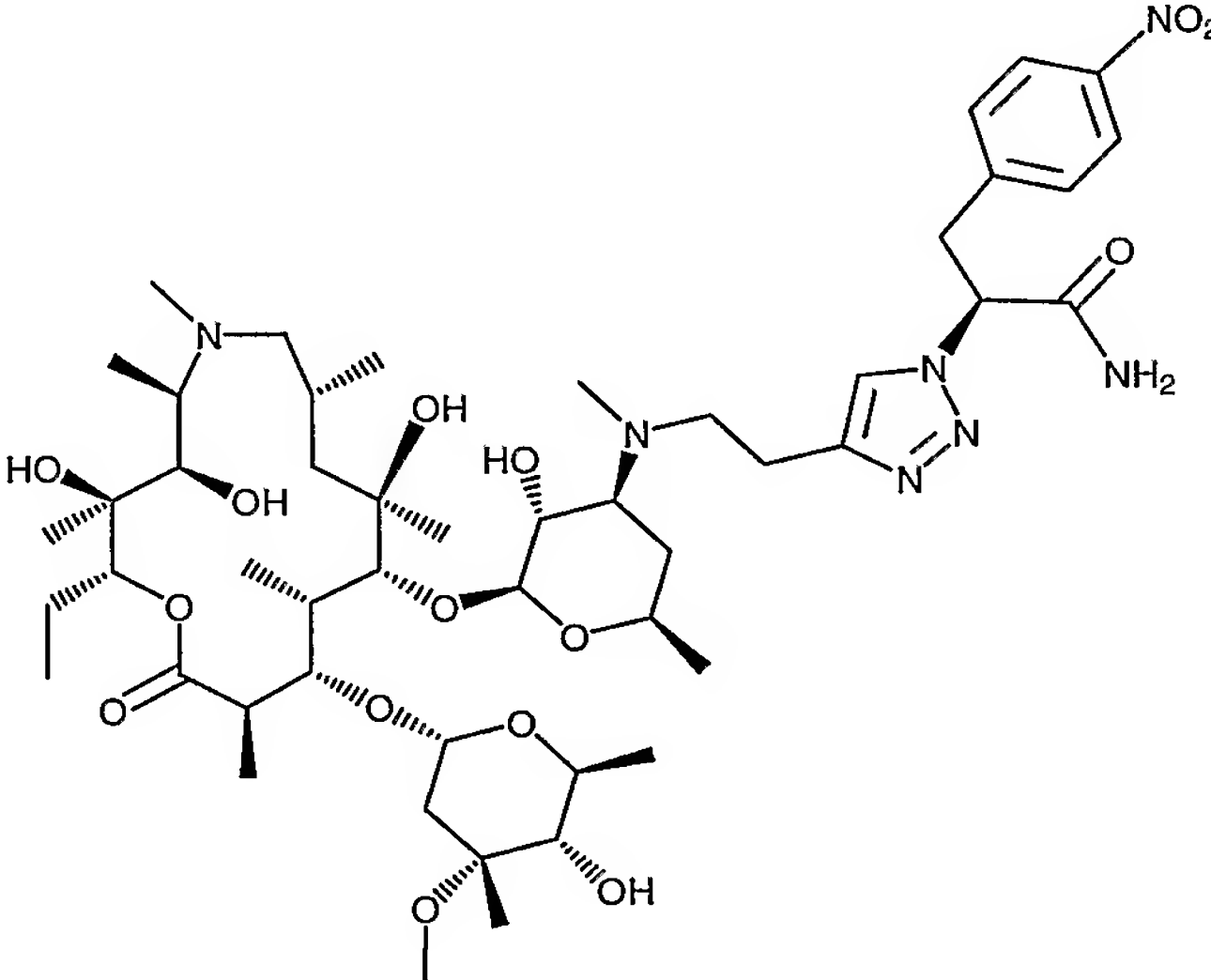
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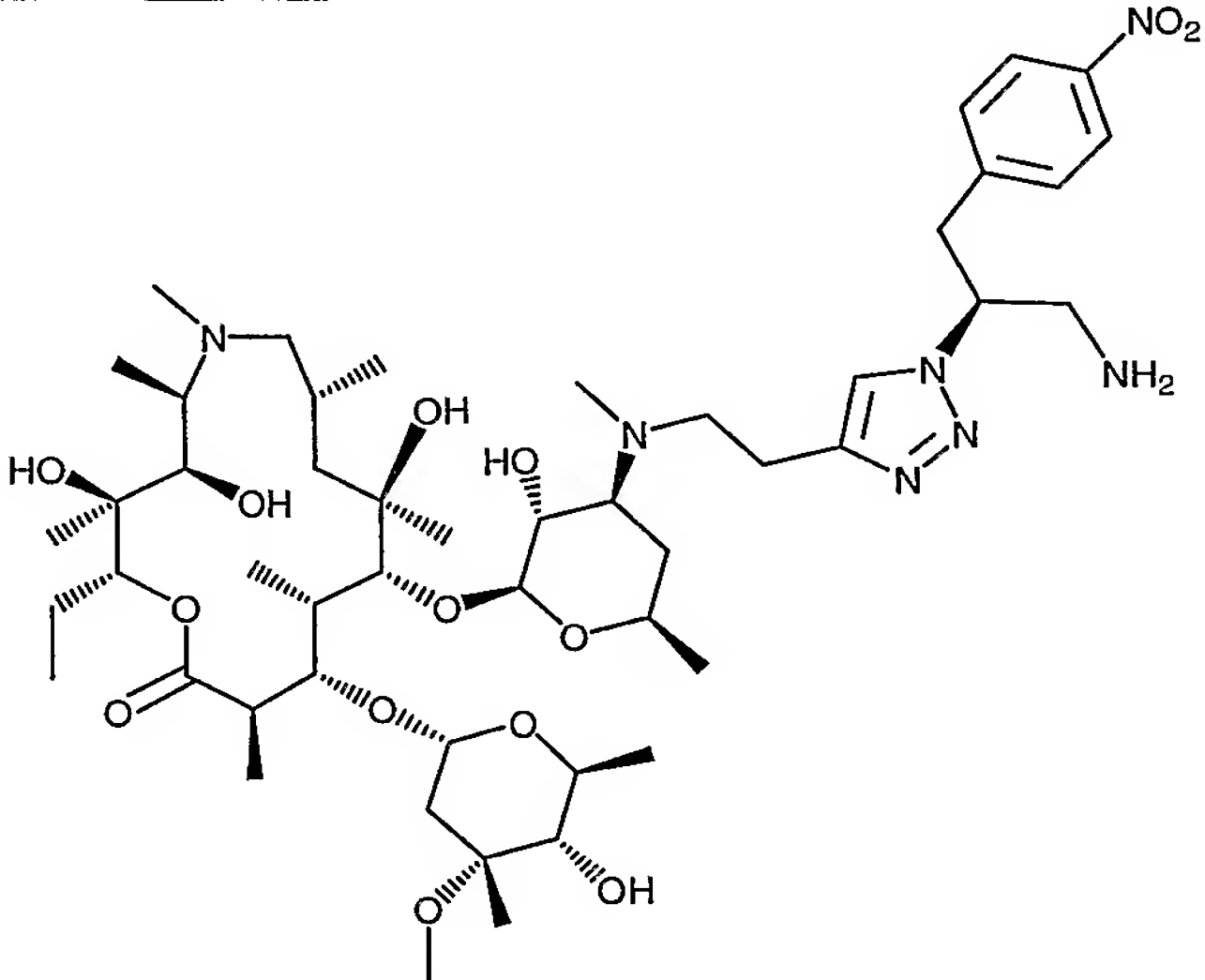
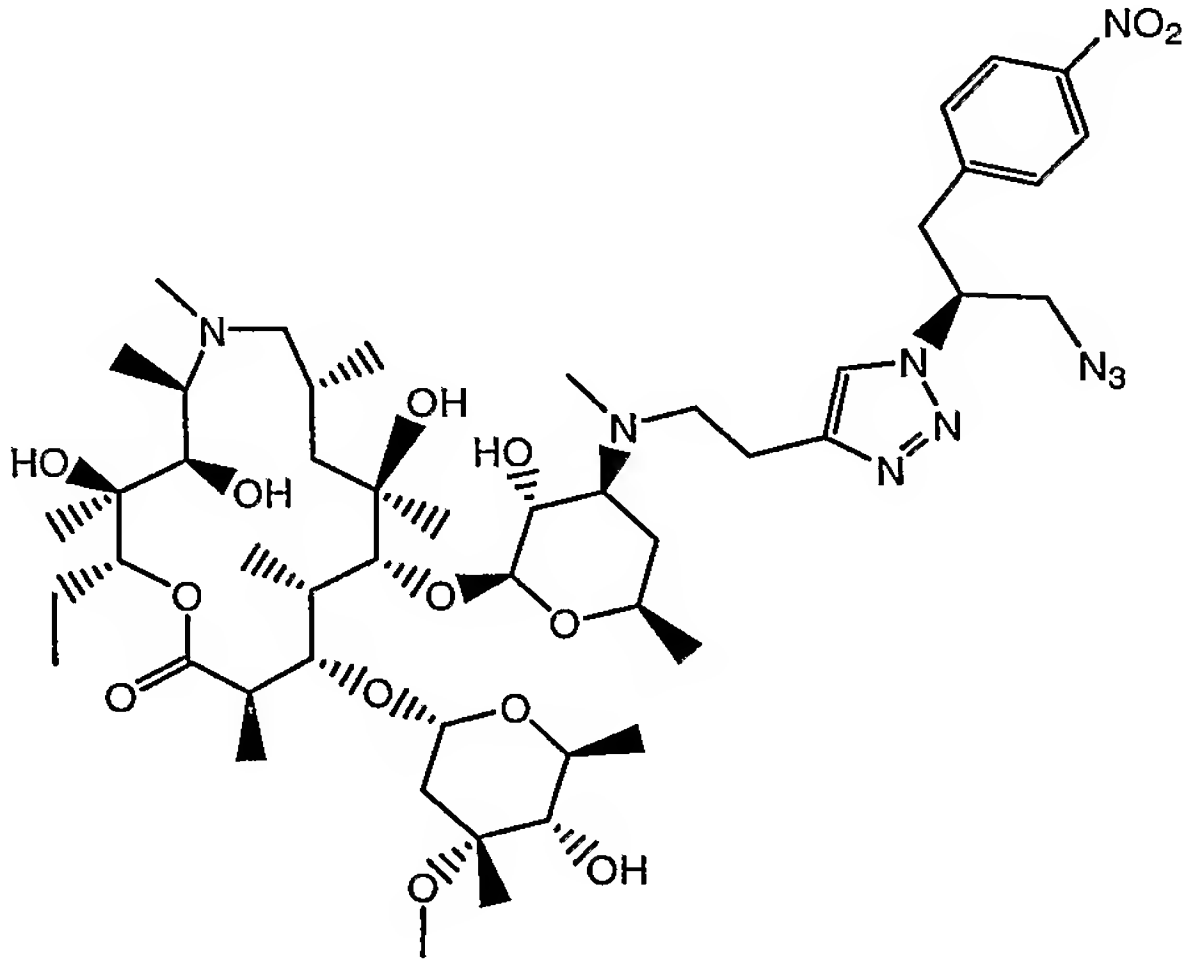
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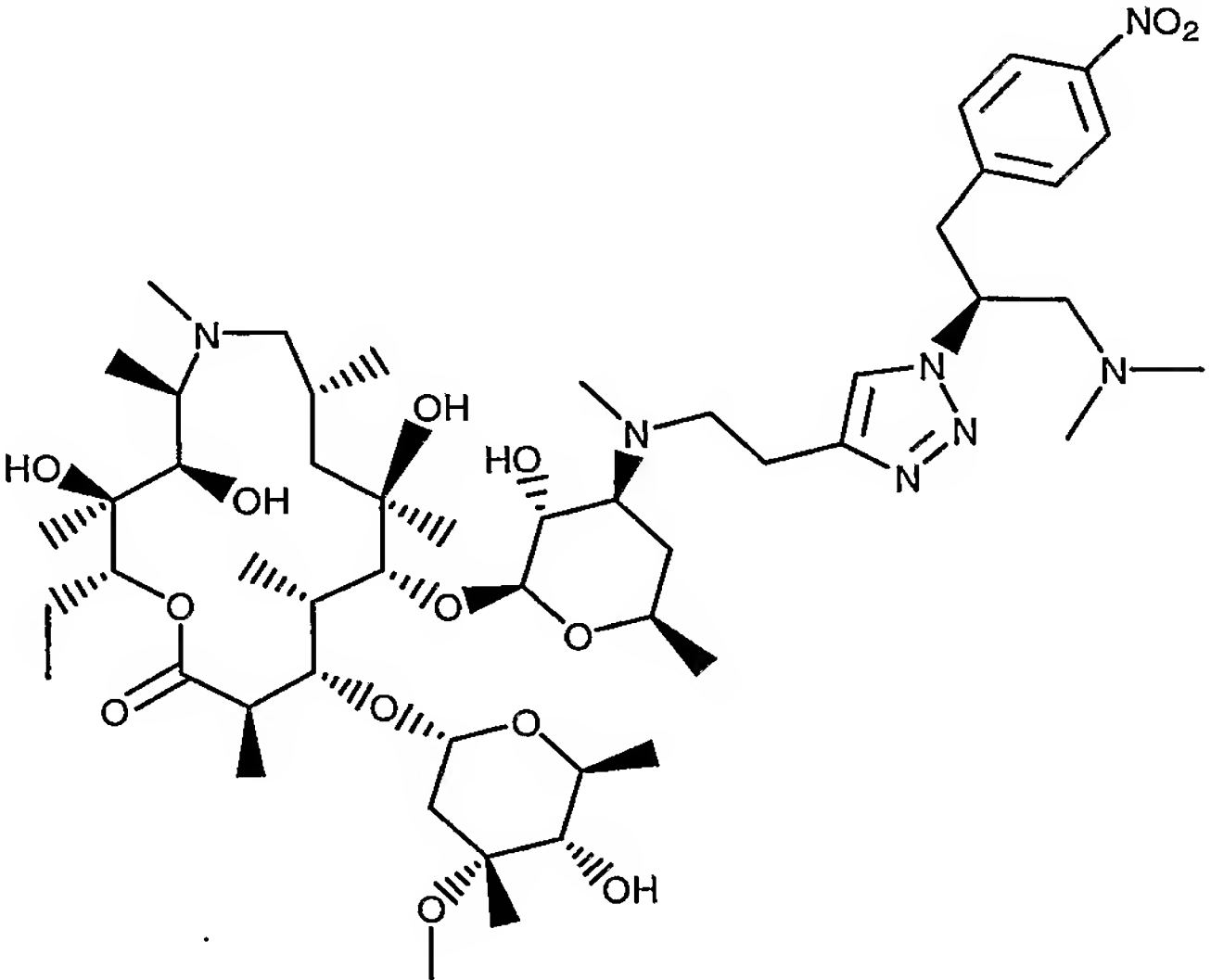
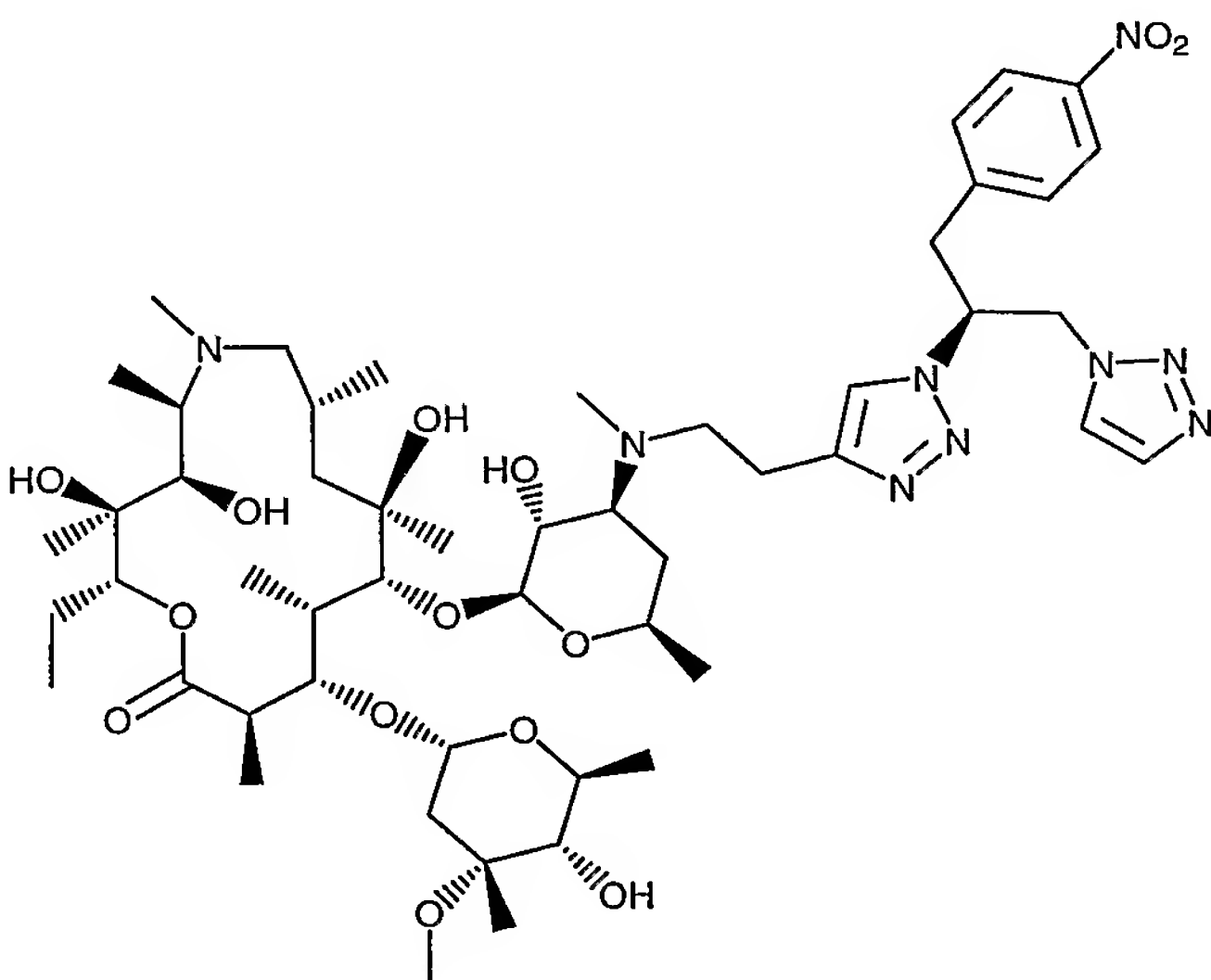
215	 <p>Chemical structure of compound 215, a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring and a pyridine moiety.</p>
216	 <p>Chemical structure of compound 216, a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring and a sulfonamide moiety.</p>

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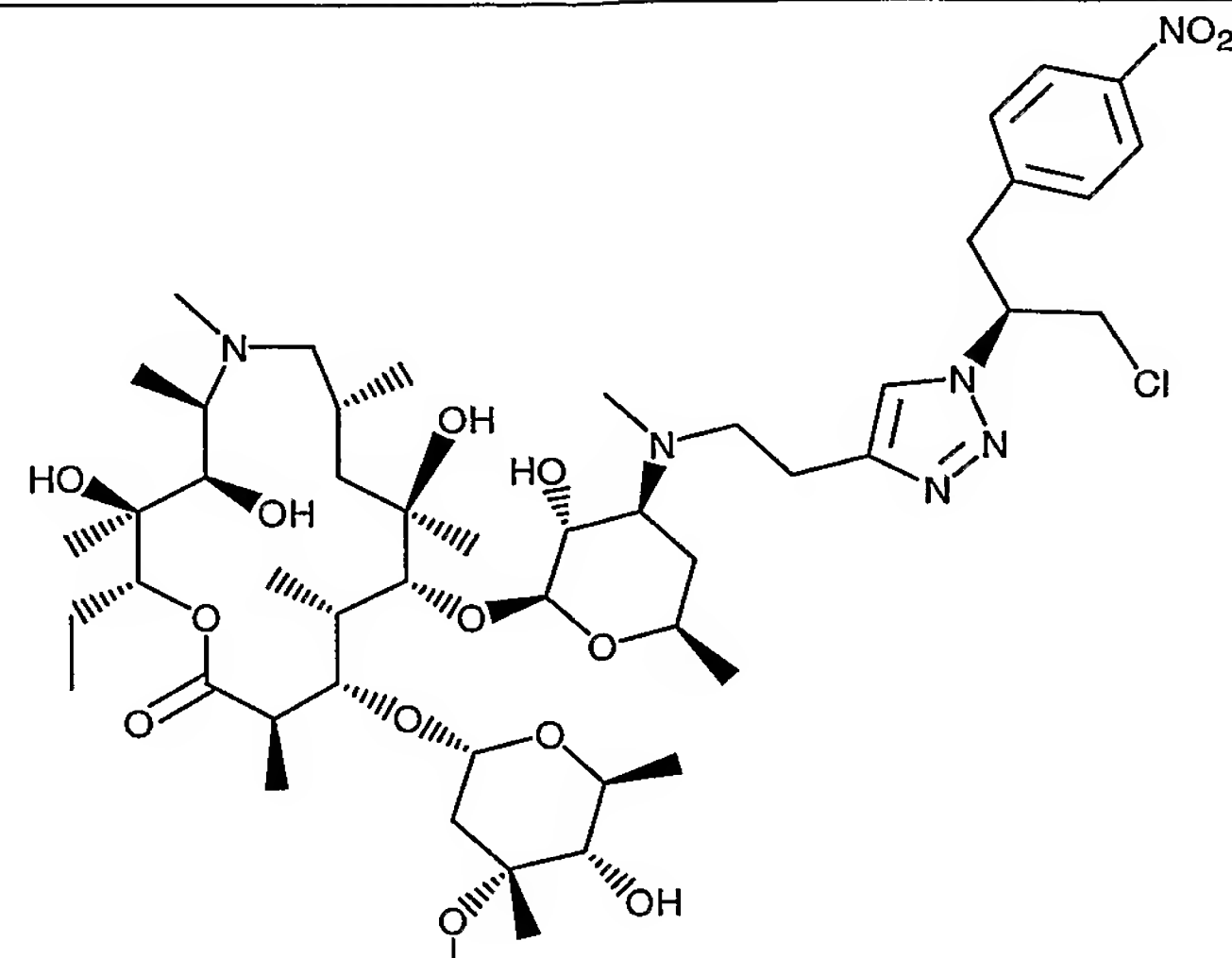
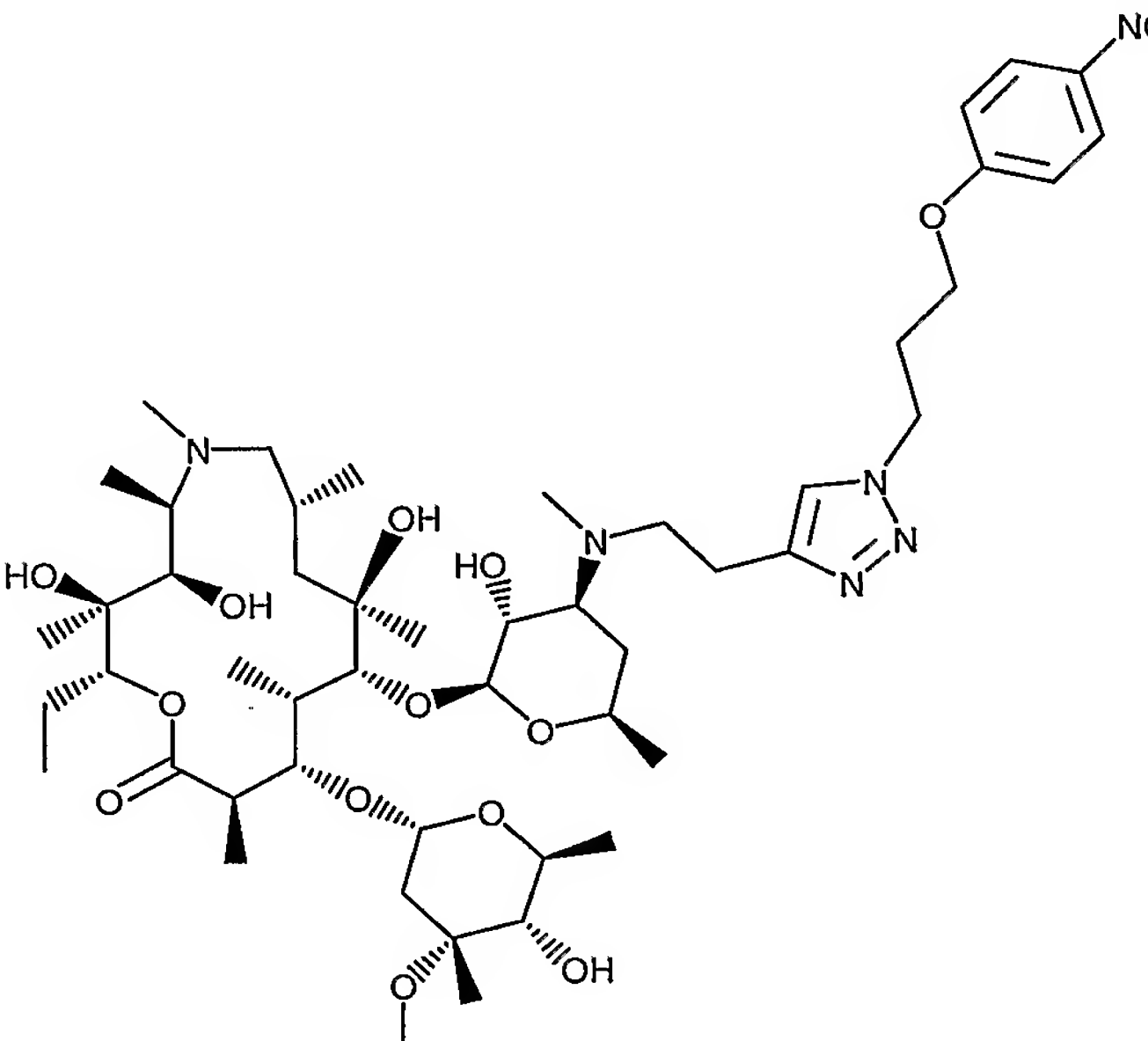
217	 <p>Chemical structure 217 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring, a 4-nitrophenyl group, and a carboxylic acid group.</p>
218	 <p>Chemical structure 218 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring, a 4-nitrophenyl group, and an amide group.</p>

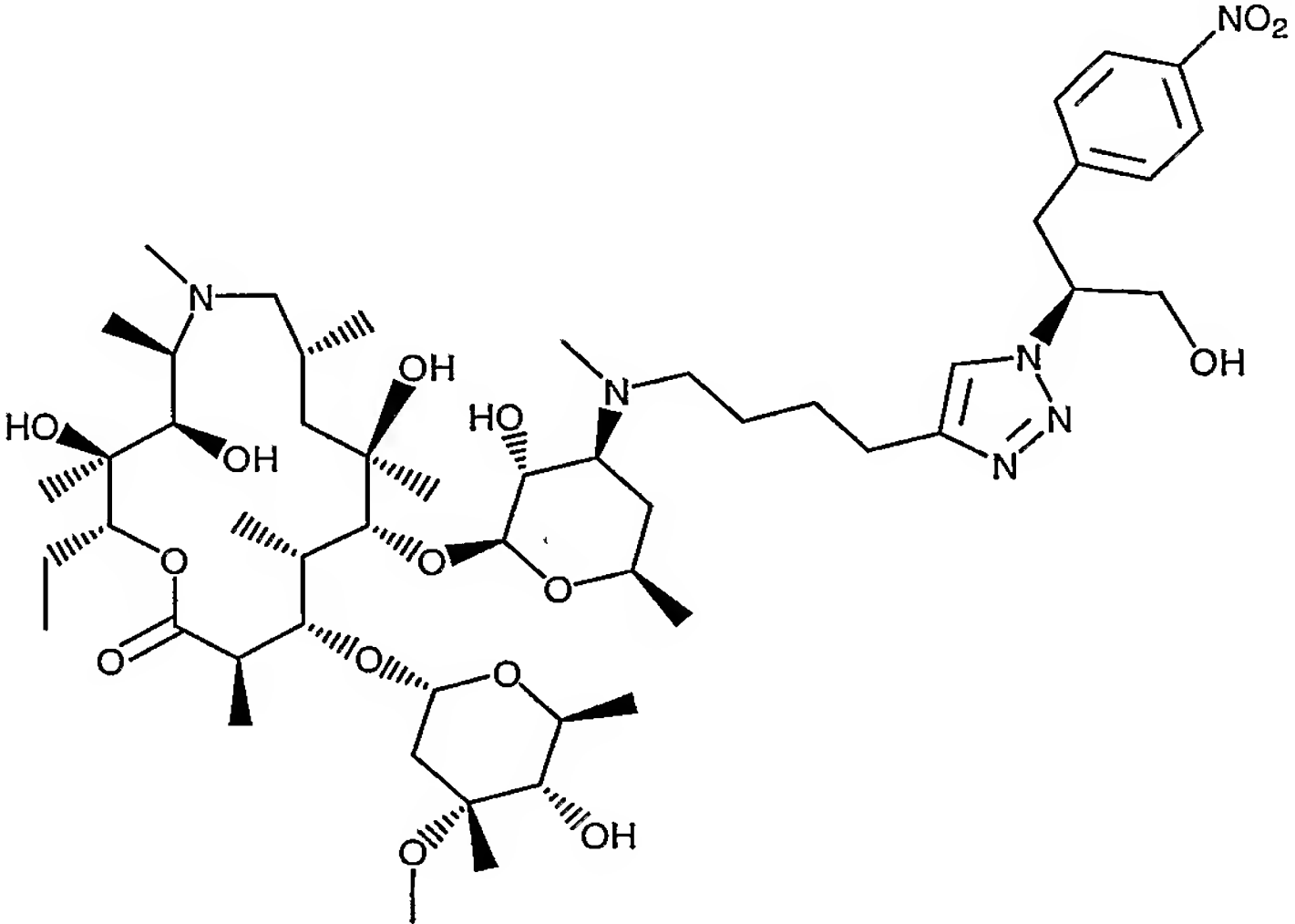
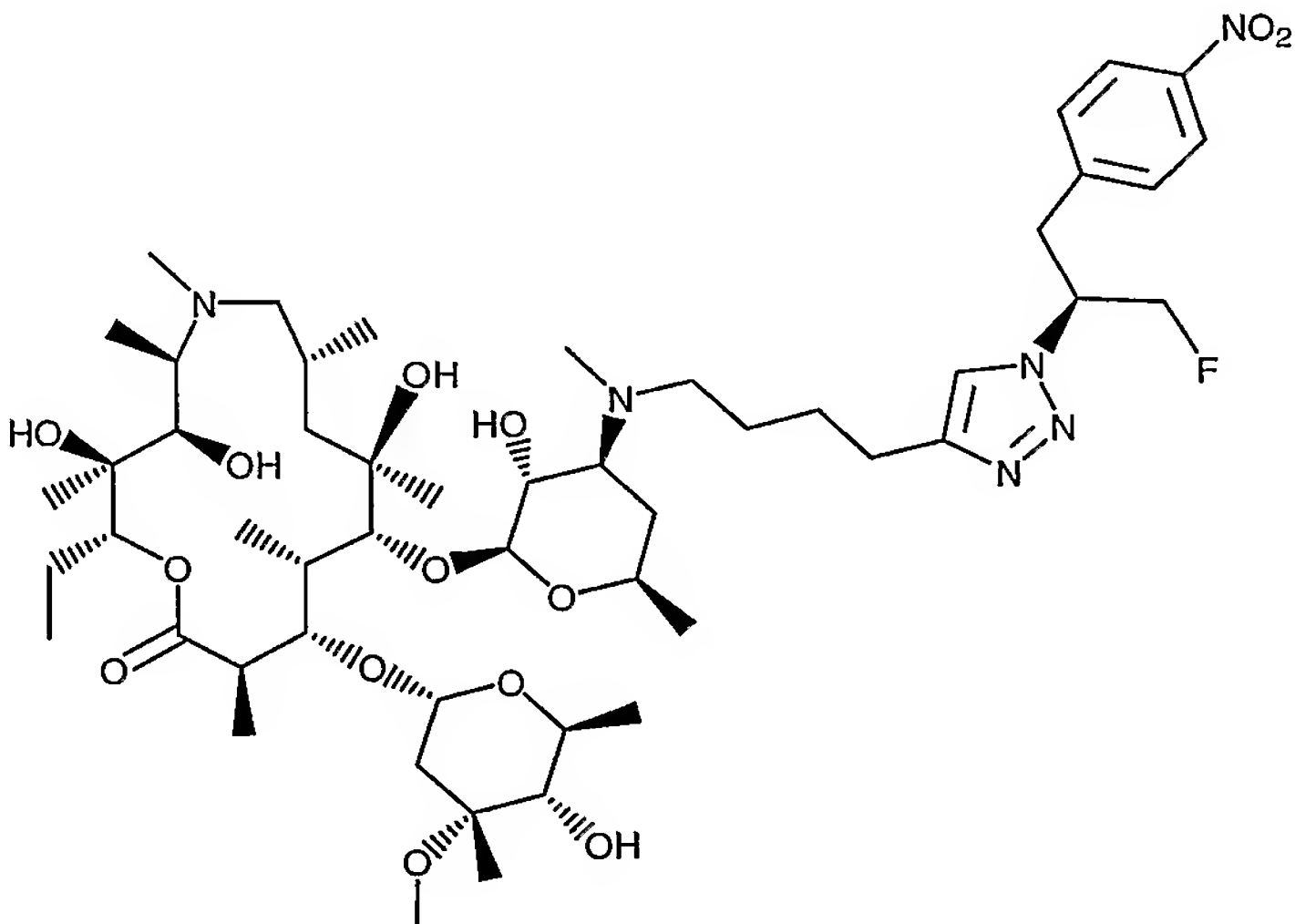
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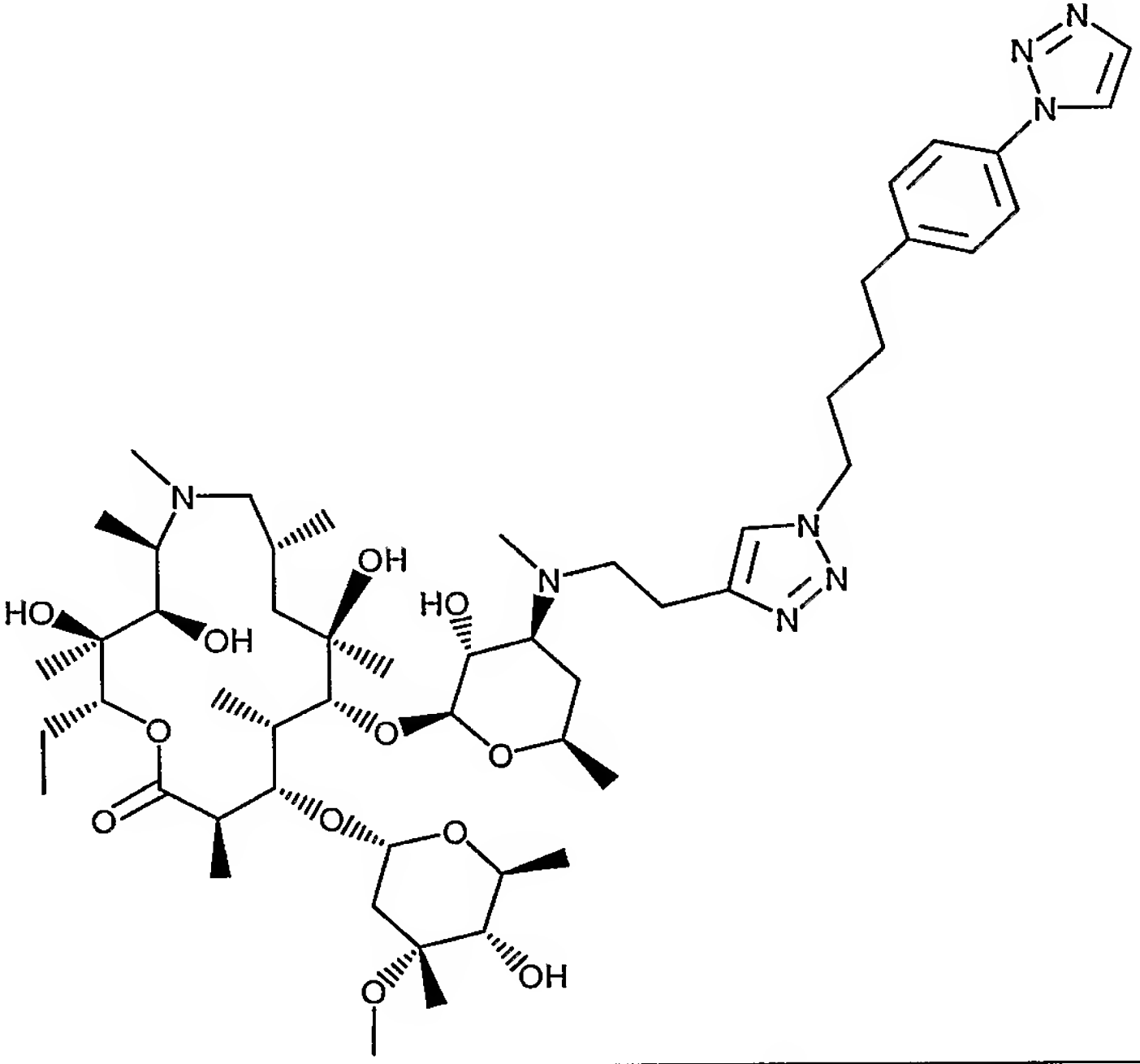
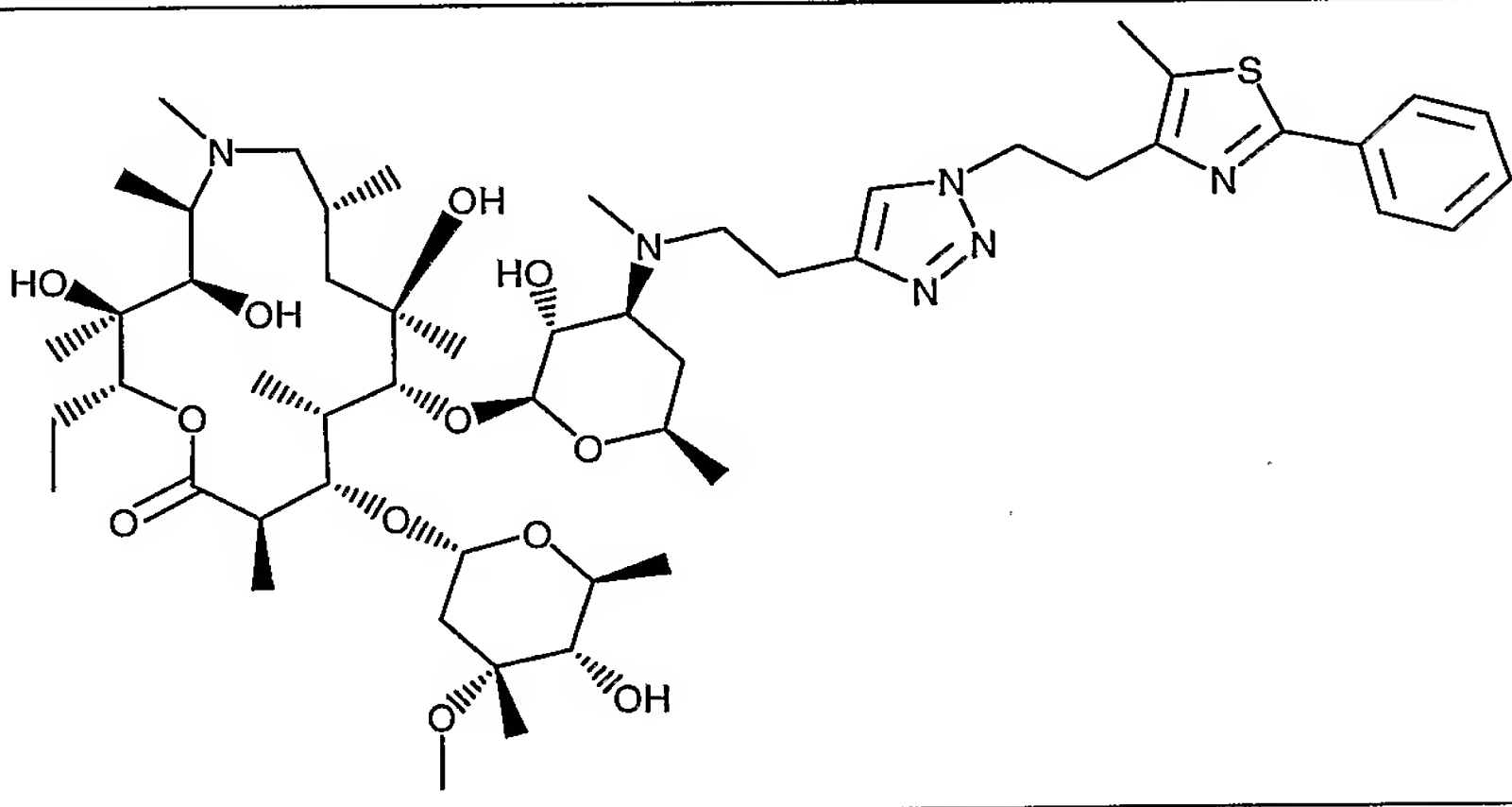
225	 <p>Chemical structure 225 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a methoxy group. The molecule is substituted with a 4-nitrophenyl group and a 1,2,3-triazole ring, which is further substituted with an amino group (NH₂).</p>
226	 <p>Chemical structure 226 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a methoxy group. The molecule is substituted with a 4-nitrophenyl group and a 1,2,3-triazole ring, which is further substituted with an azido group (N₃).</p>

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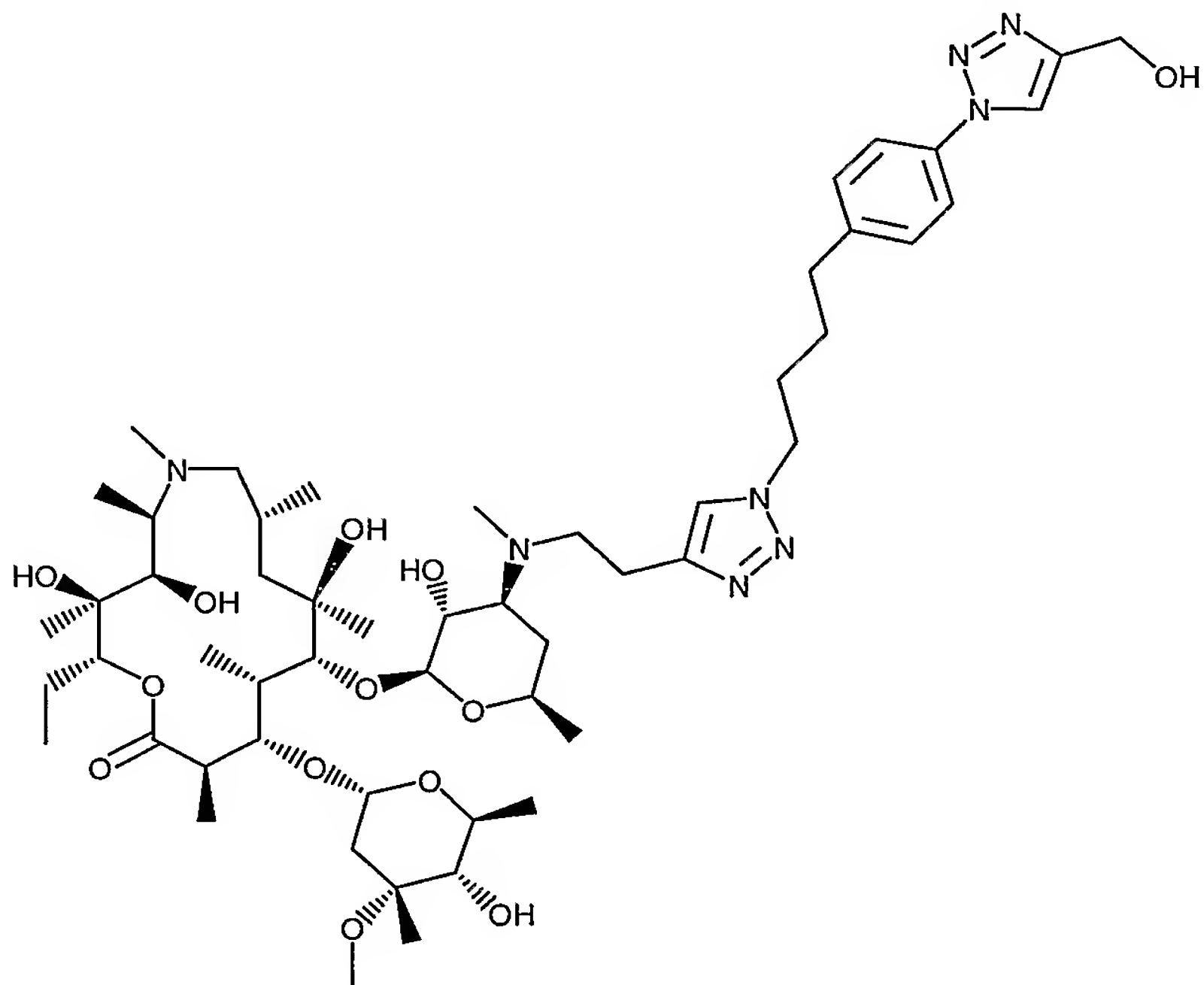
229	 <p>Chemical structure of compound 229. It features a complex polycyclic core with multiple hydroxyl groups and a methylated nitrogen. A side chain includes a 1,2,4-triazole ring connected to a 4-nitrophenyl group via a benzyl-like linker, and a 2-chloroethyl group.</p>
230	 <p>Chemical structure of compound 230. It features a complex polycyclic core with multiple hydroxyl groups and a methylated nitrogen. A side chain includes a 1,2,4-triazole ring connected to a 4-nitrophenyl group via a 3-(4-nitrophenoxy)propyl linker.</p>

231	 <p>Chemical structure of compound 231. It features a complex polycyclic core with multiple hydroxyl groups and a methyl group. A side chain includes a 1,2,4-triazole ring connected to a 4-nitrophenyl group via a methylene bridge. The triazole ring is also connected to a 1-hydroxypropyl group.</p>
232	 <p>Chemical structure of compound 232. It is similar to compound 231, but the side chain is modified: the 1-hydroxypropyl group is replaced by a 1-fluoroethyl group.</p>

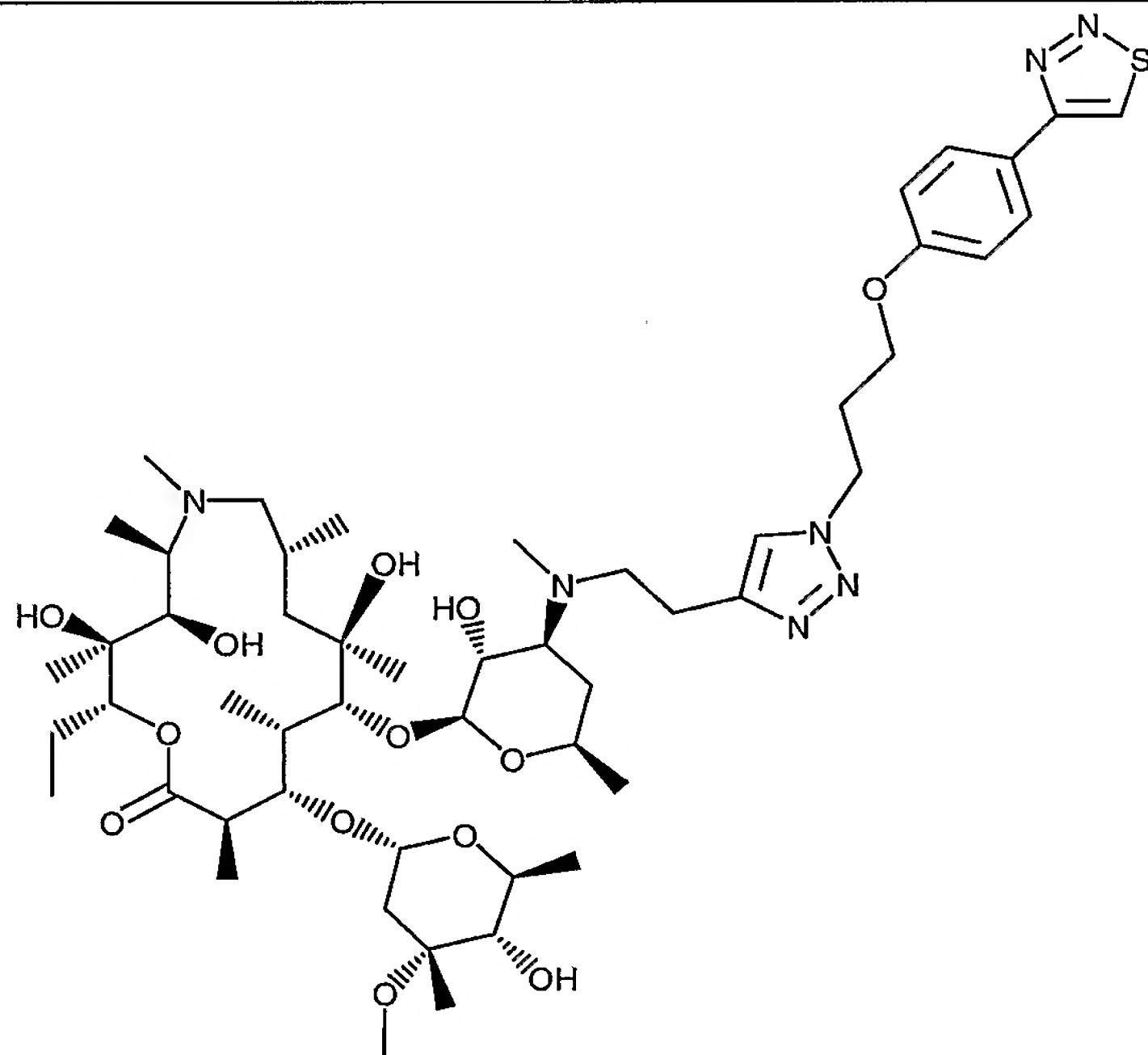
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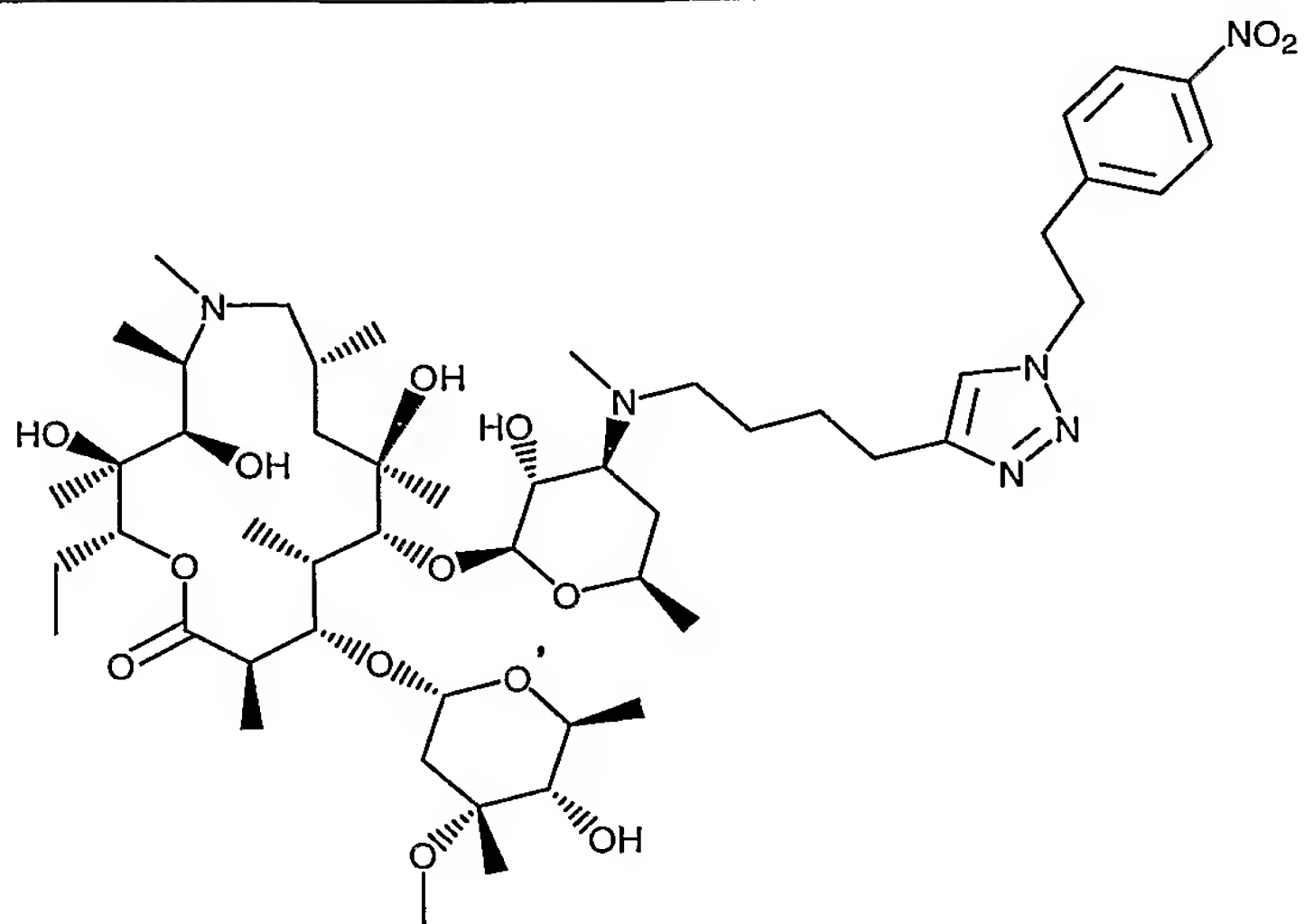


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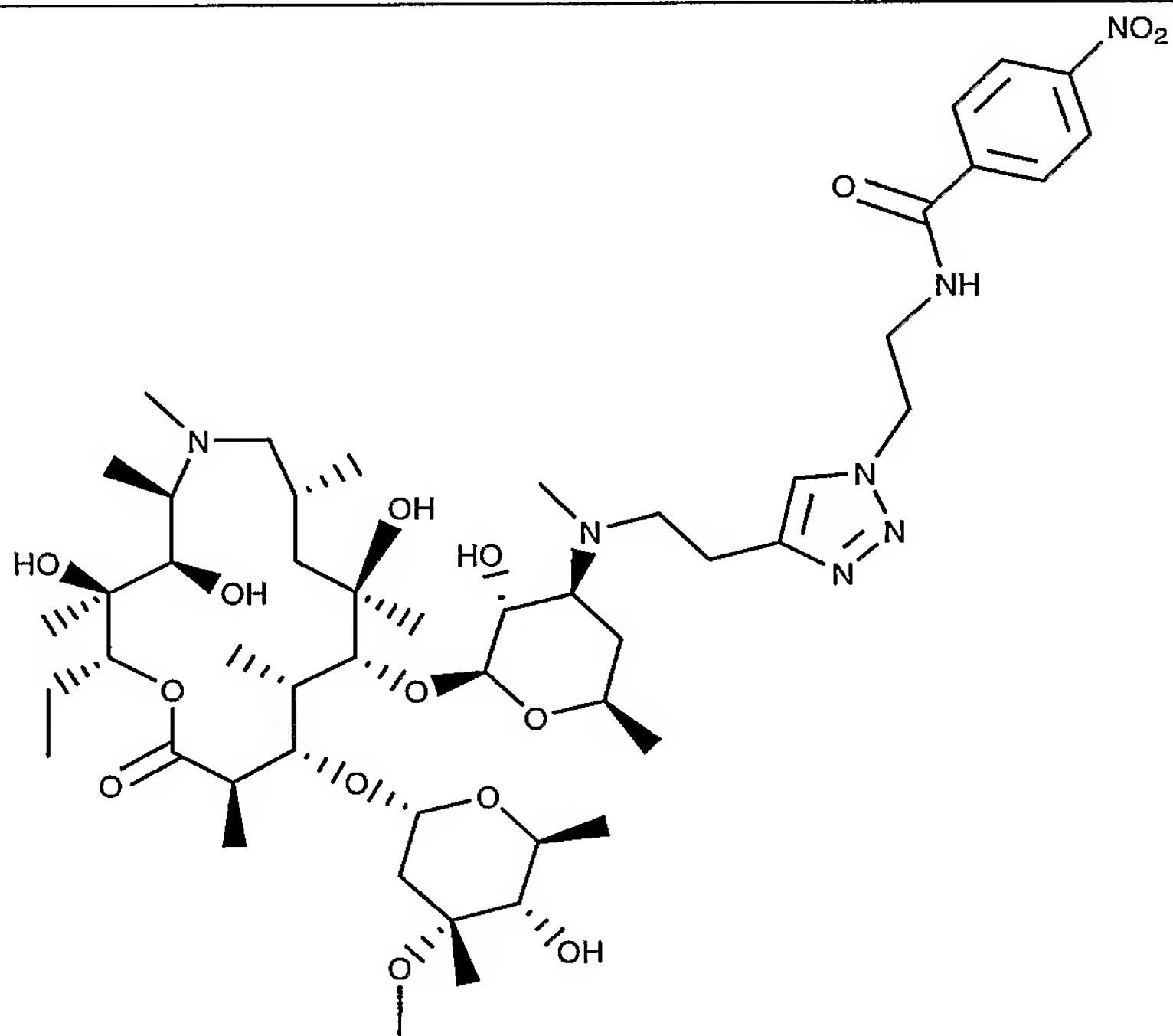


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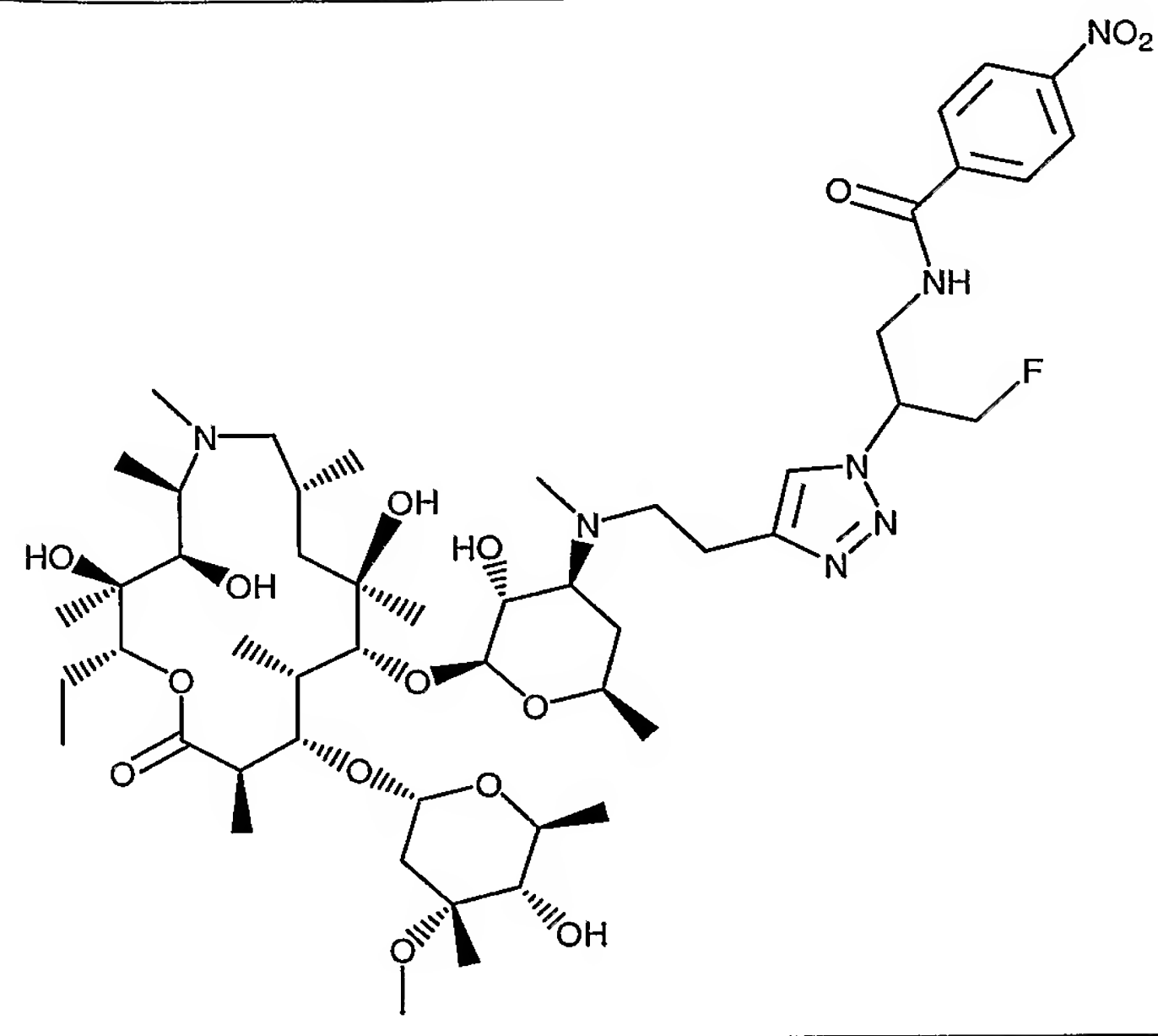
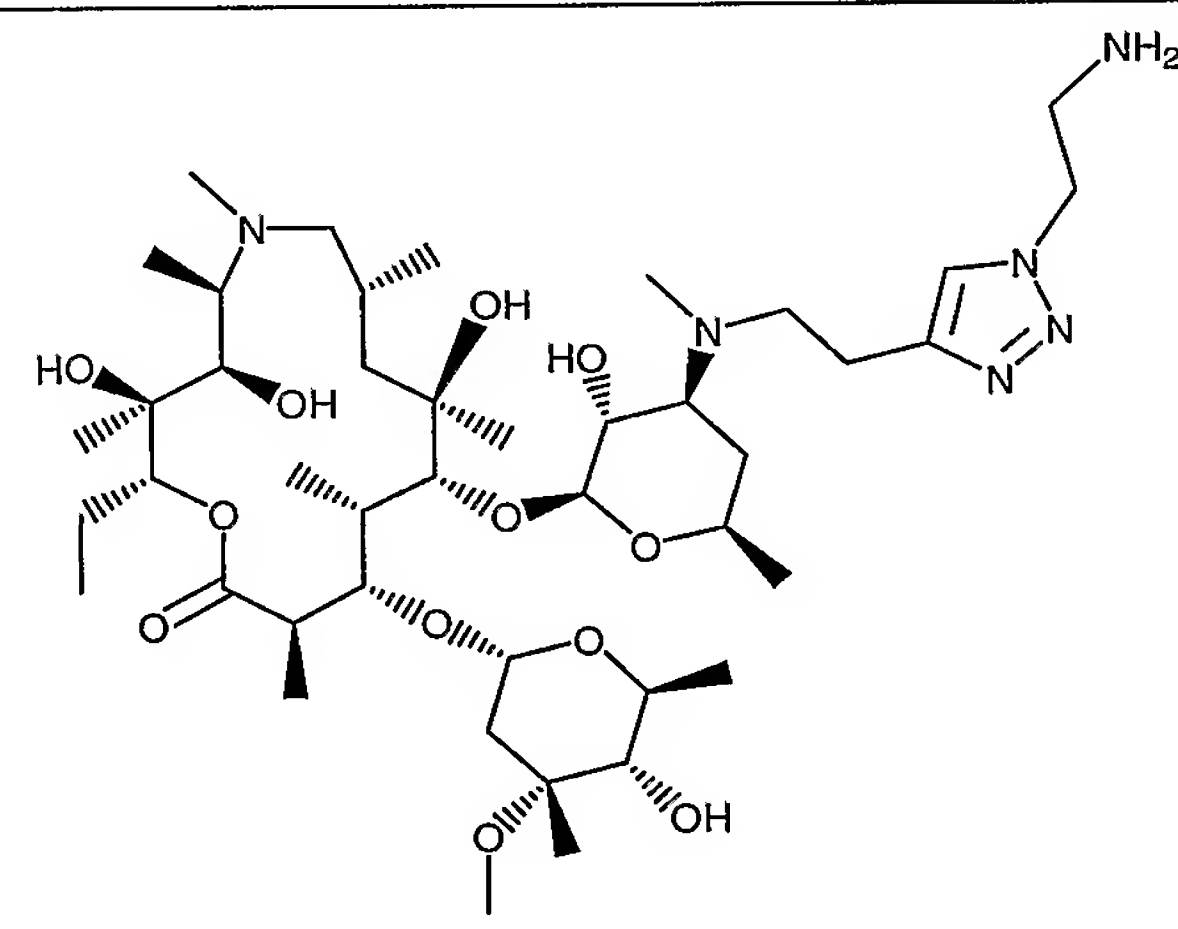
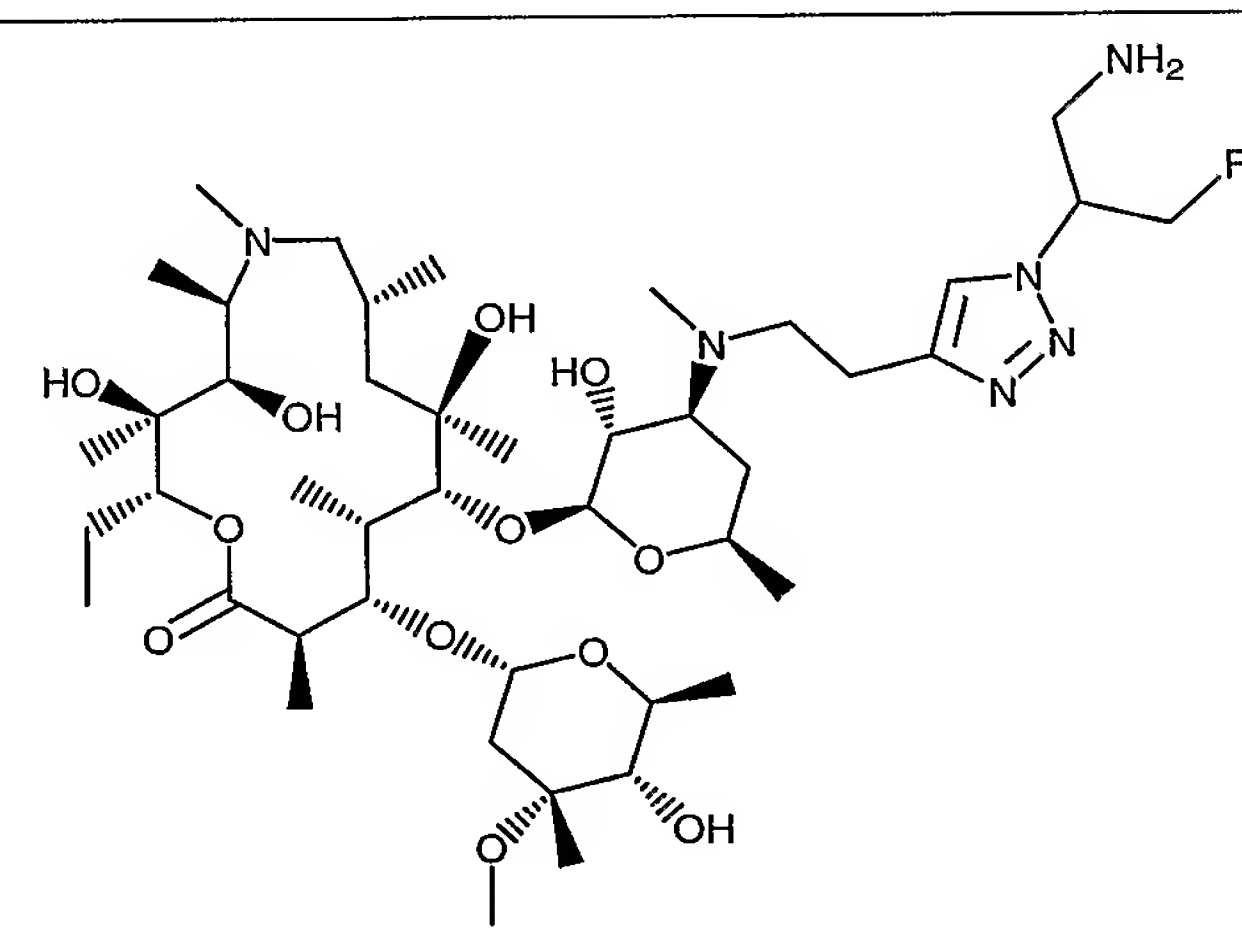
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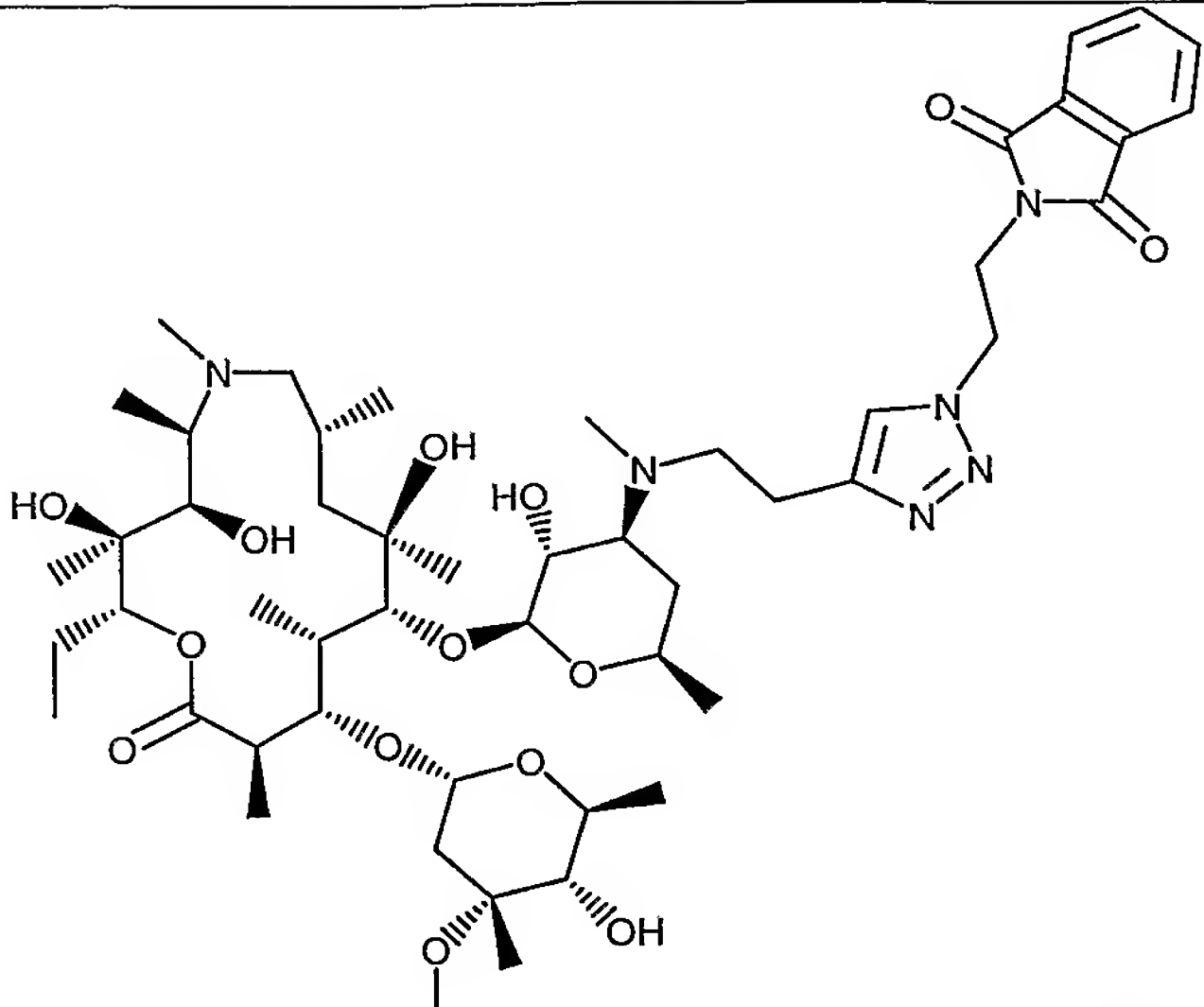
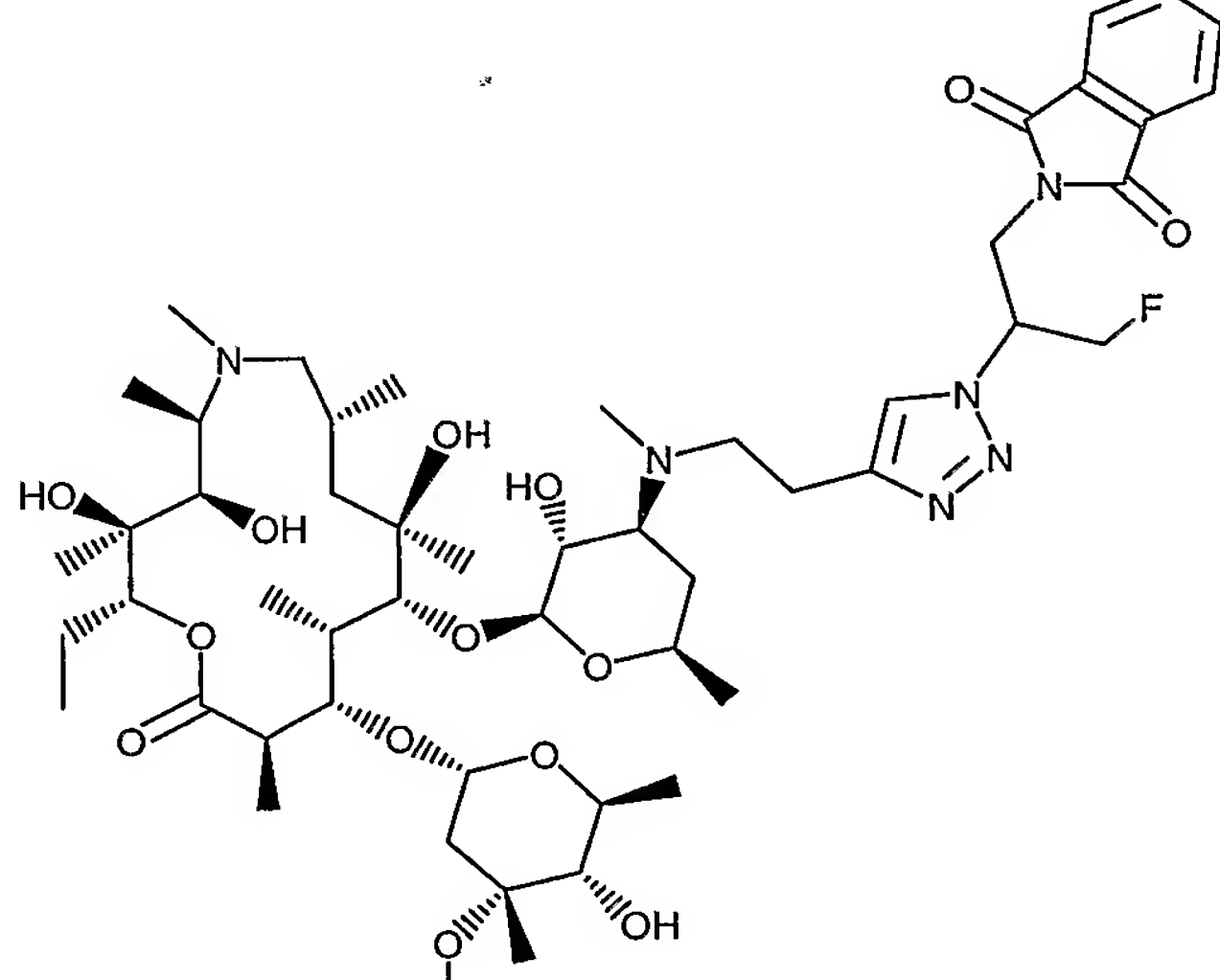
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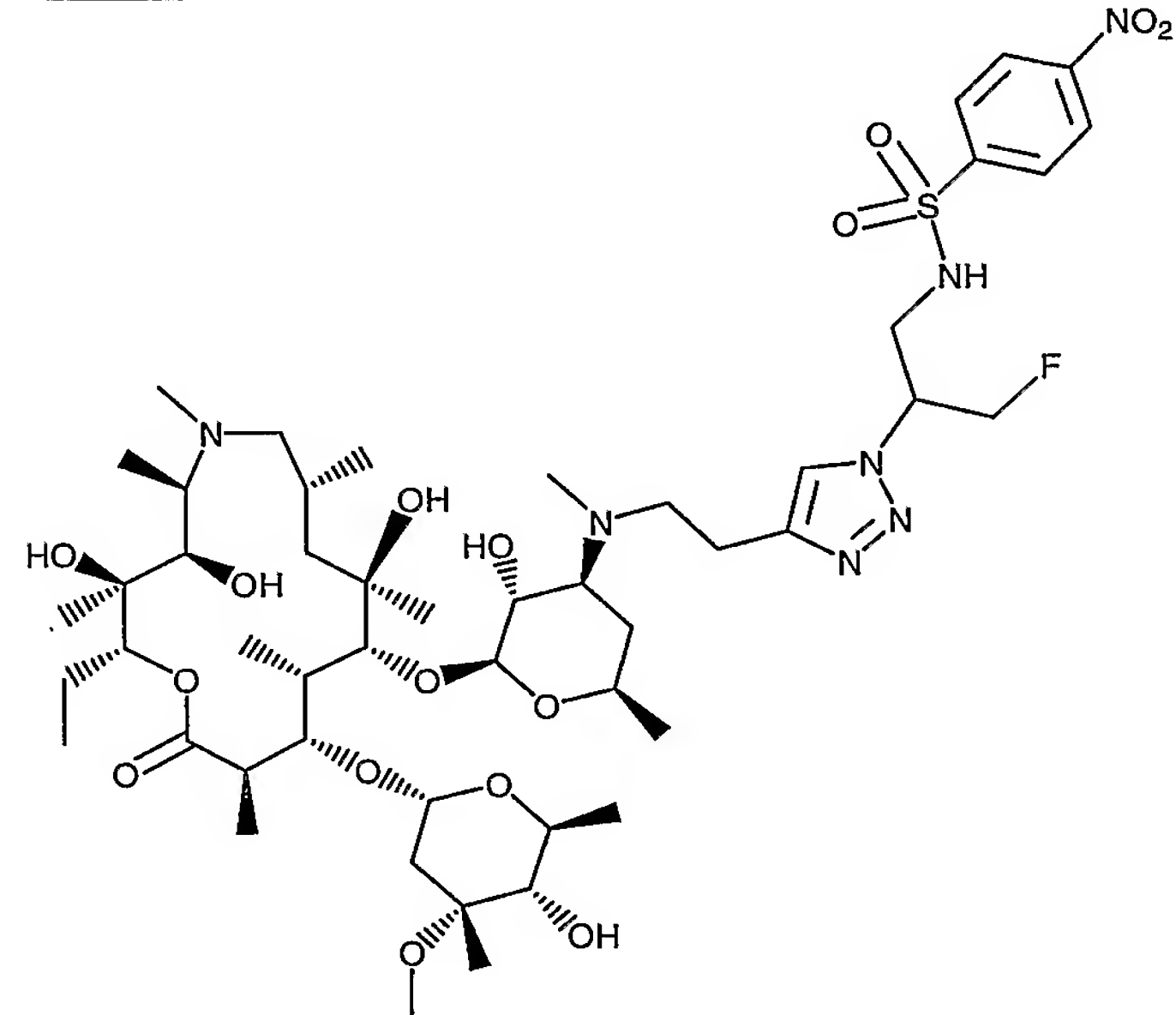
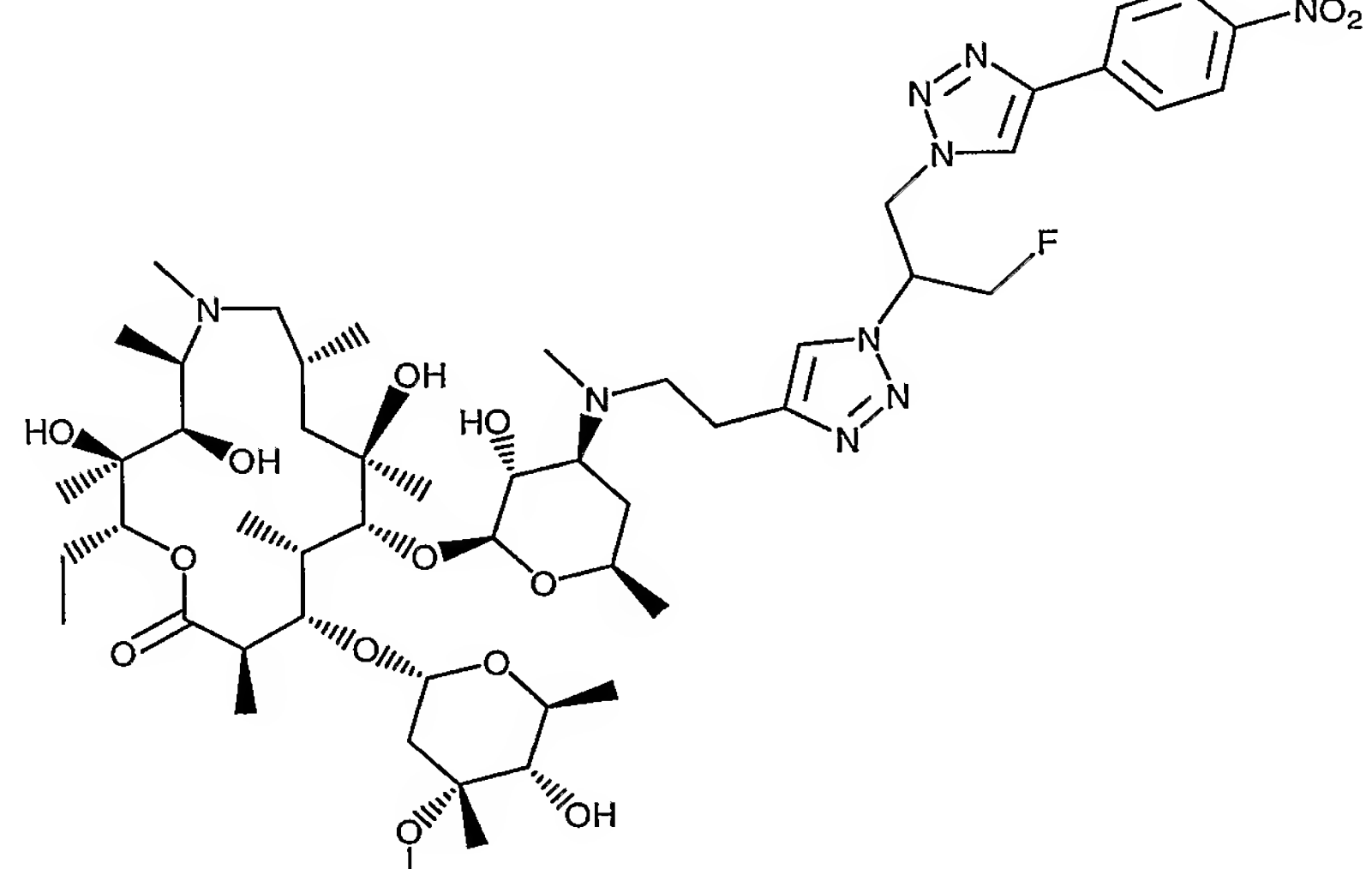


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241	 <p>Chemical structure 241 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a methyl group. It is substituted with a 4-nitrophenyl group via an amide linkage, a 2-fluoroethyl group, and a 1,2,4-triazole ring.</p>
242	 <p>Chemical structure 242 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a methyl group. It is substituted with a 2-aminoethyl group and a 1,2,4-triazole ring.</p>
243	 <p>Chemical structure 243 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a methyl group. It is substituted with a 2-aminoethyl group, a 2-fluoroethyl group, and a 1,2,4-triazole ring.</p>

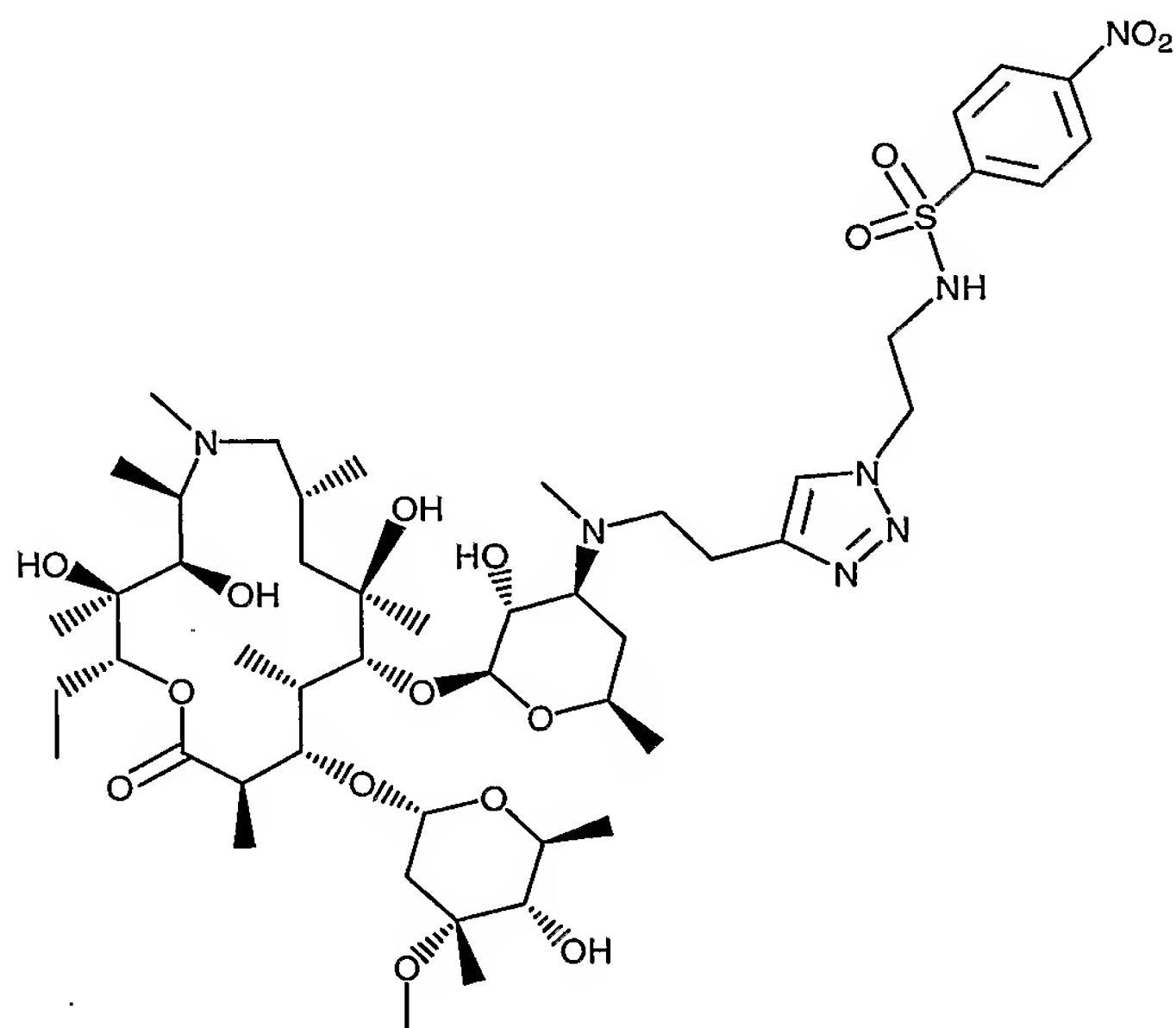
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244	 <p>Chemical structure 244 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring and a phthalimide group. The structure is highly detailed, showing stereochemistry and various functional groups.</p>
245	 <p>Chemical structure 245 is a complex molecule, similar to 244, but with a different side chain configuration. It includes a fluorine atom and a different phthalimide derivative. The structure is highly detailed, showing stereochemistry and various functional groups.</p>

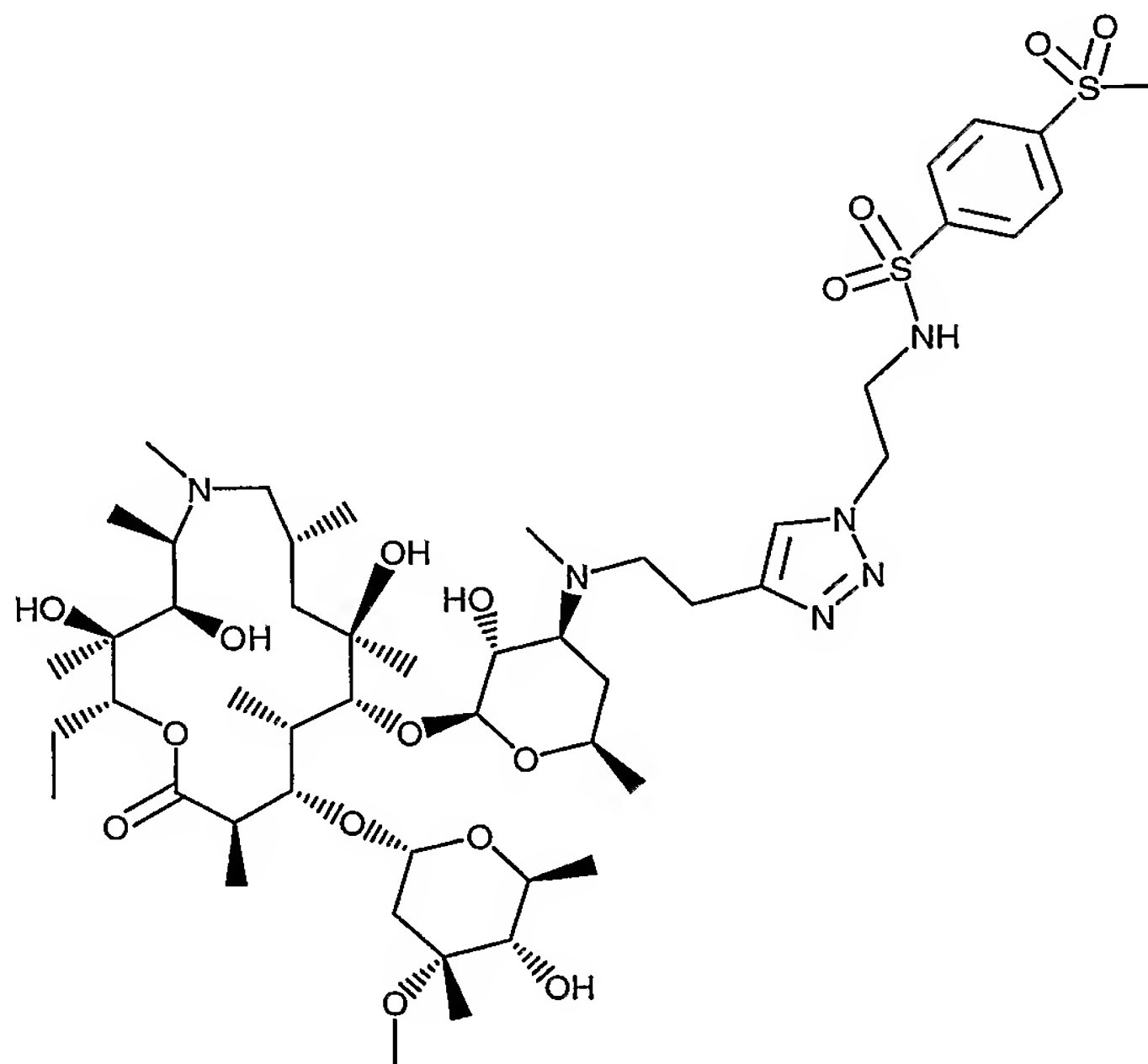
246	 <p>Chemical structure 246: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a methyl group. Attached to the core is a side chain containing a 1,2,4-triazole ring, a 2-fluoroethyl group, and a 4-nitrobenzenesulfonamide group.</p>
247	 <p>Chemical structure 247: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a methyl group. Attached to the core is a side chain containing a 1,2,4-triazole ring, a 2-fluoroethyl group, and a 4-nitrophenyl group.</p>

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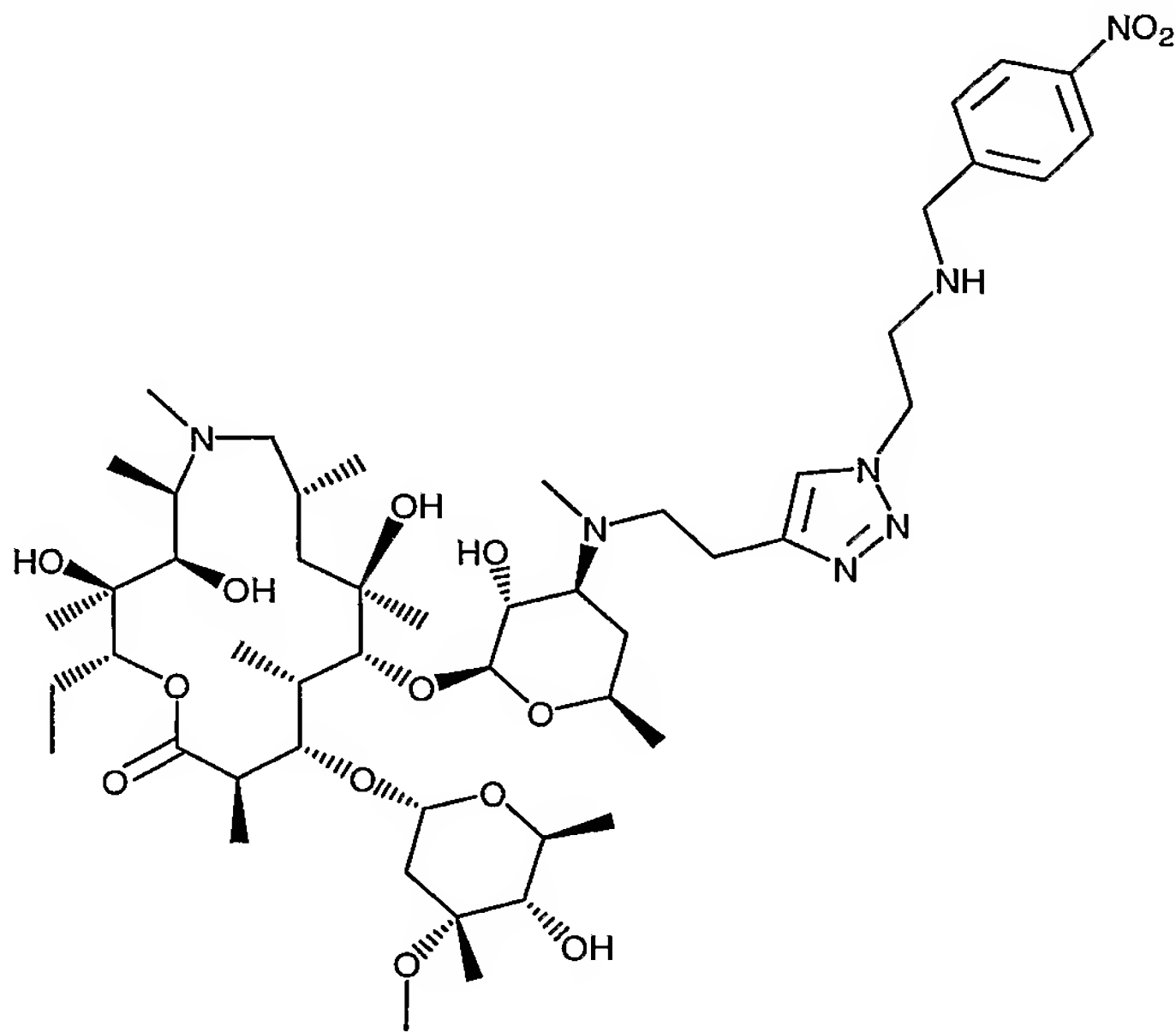
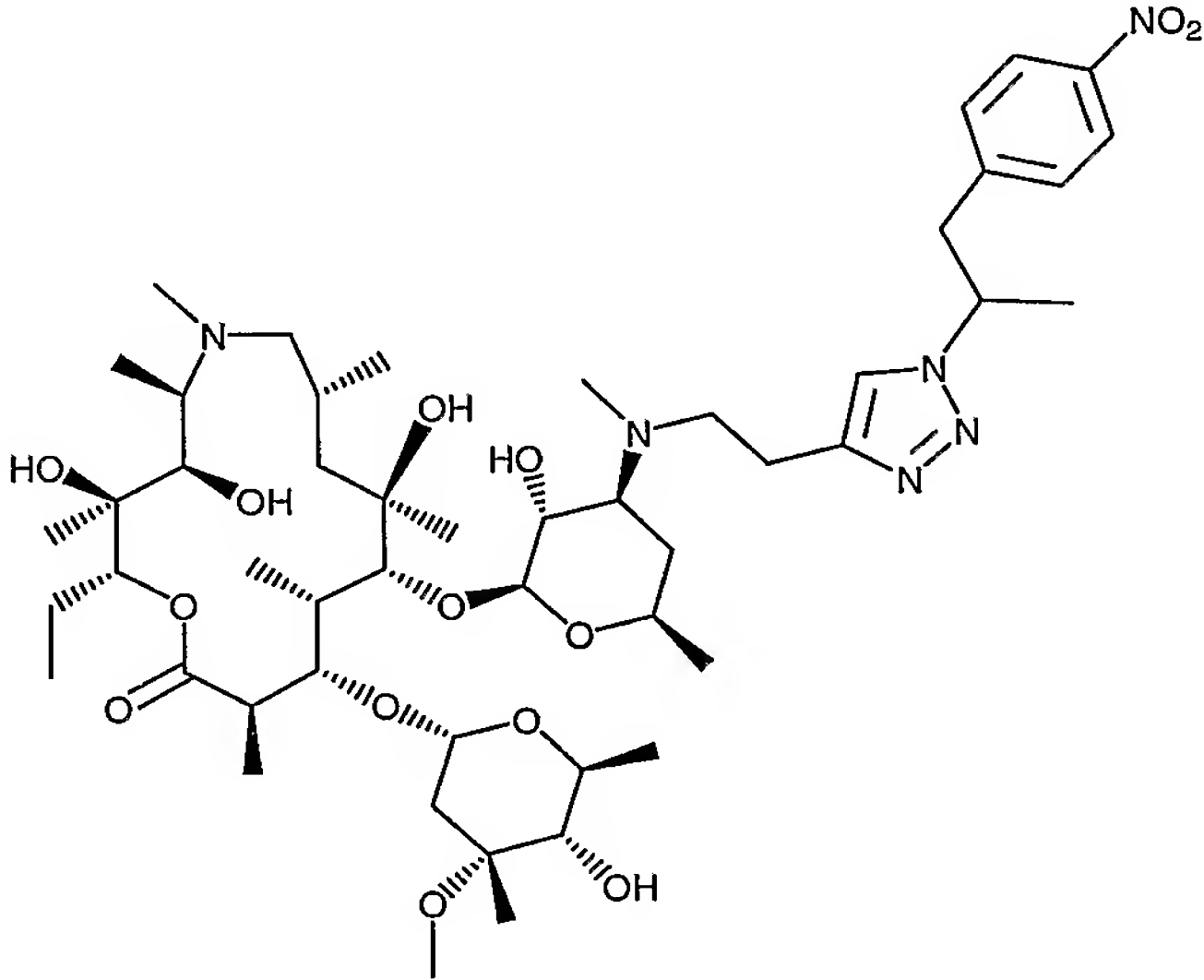
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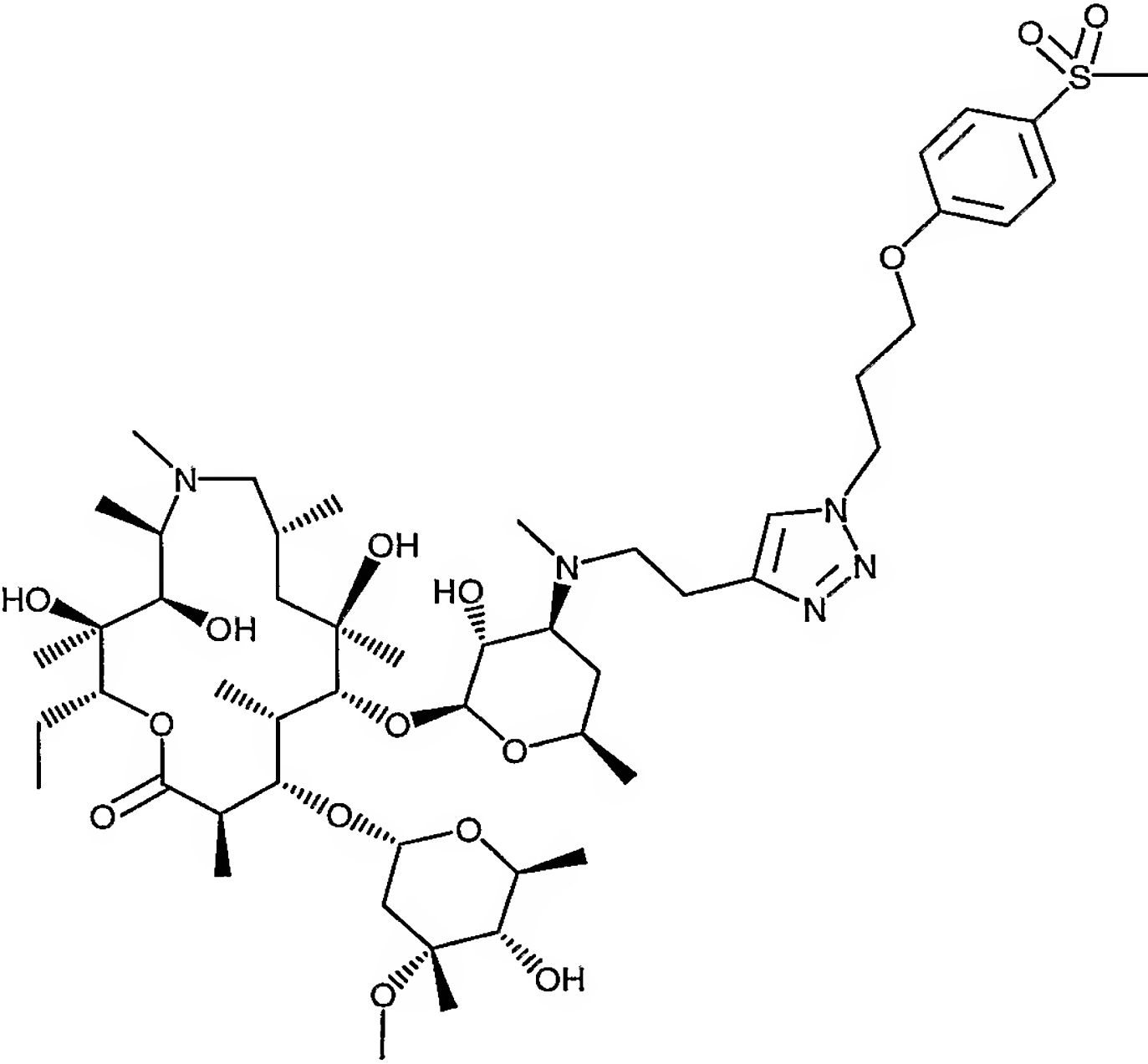
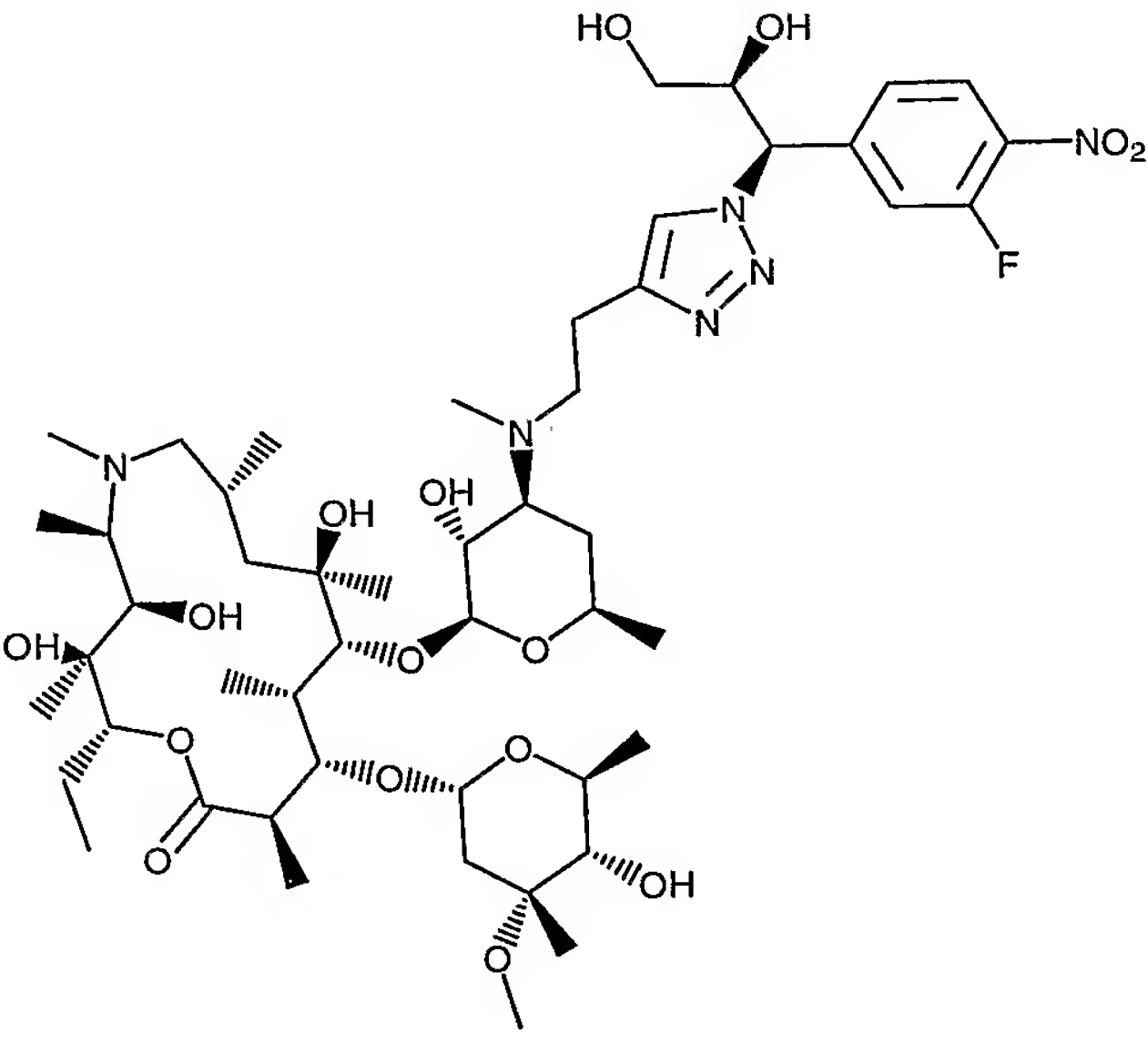
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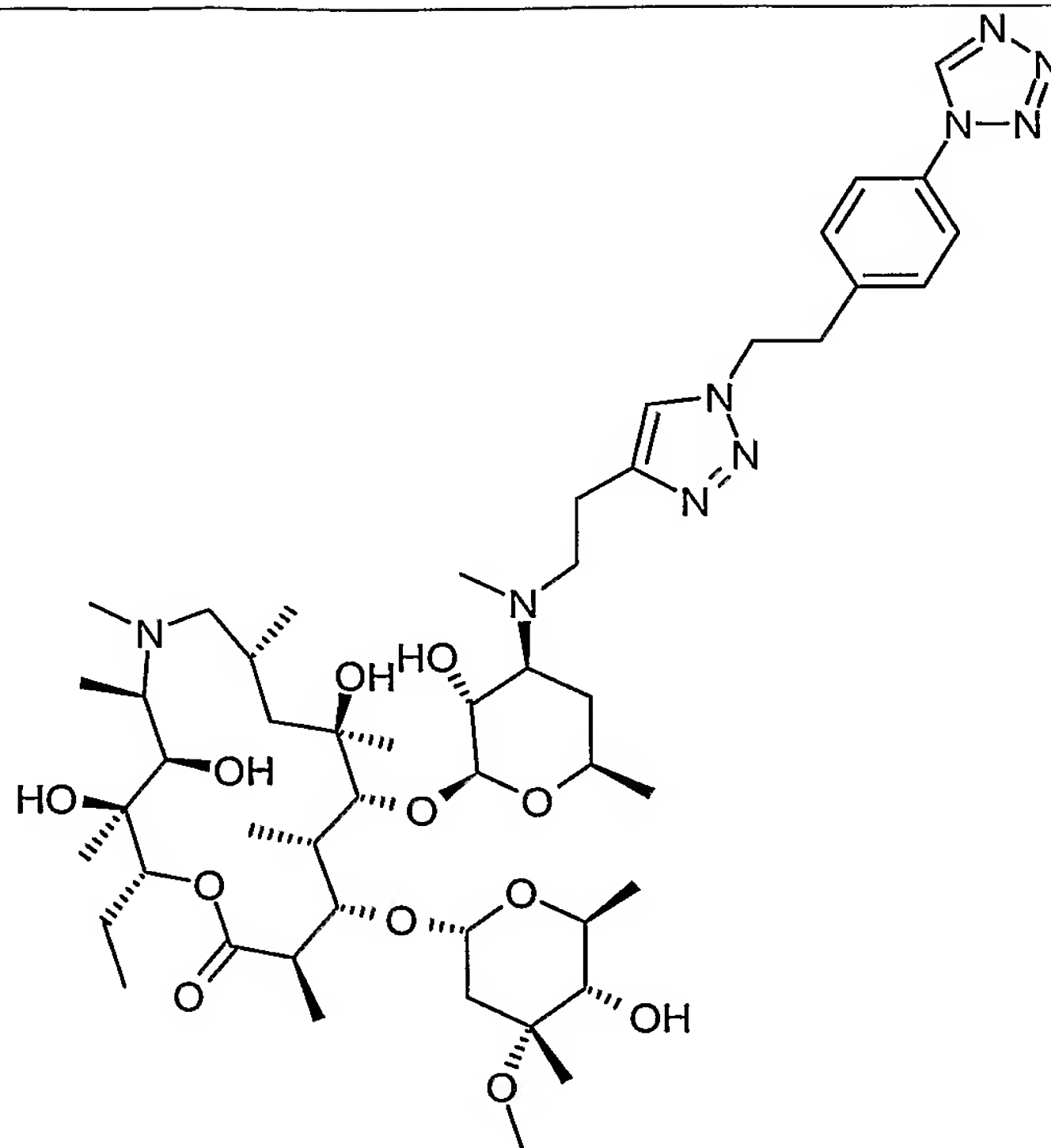
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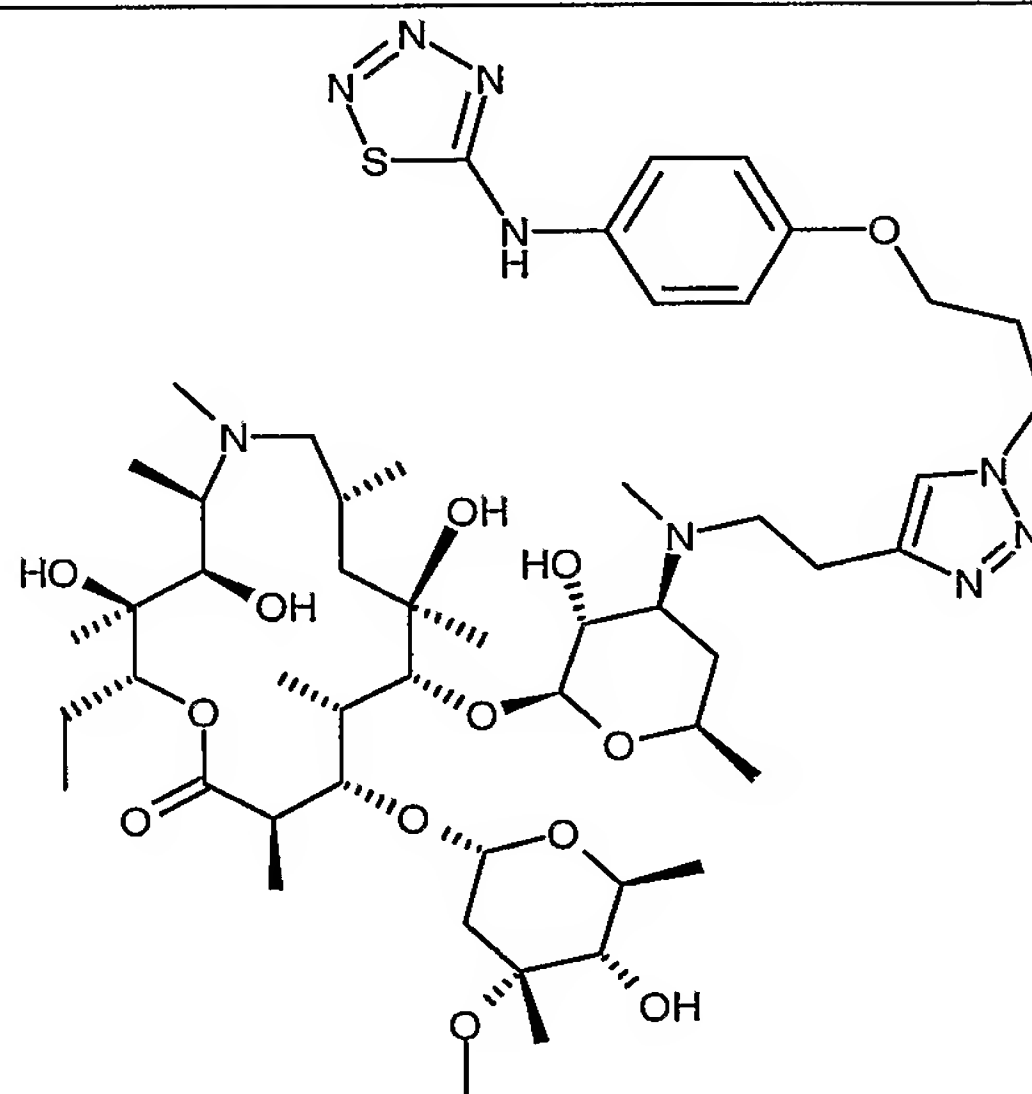
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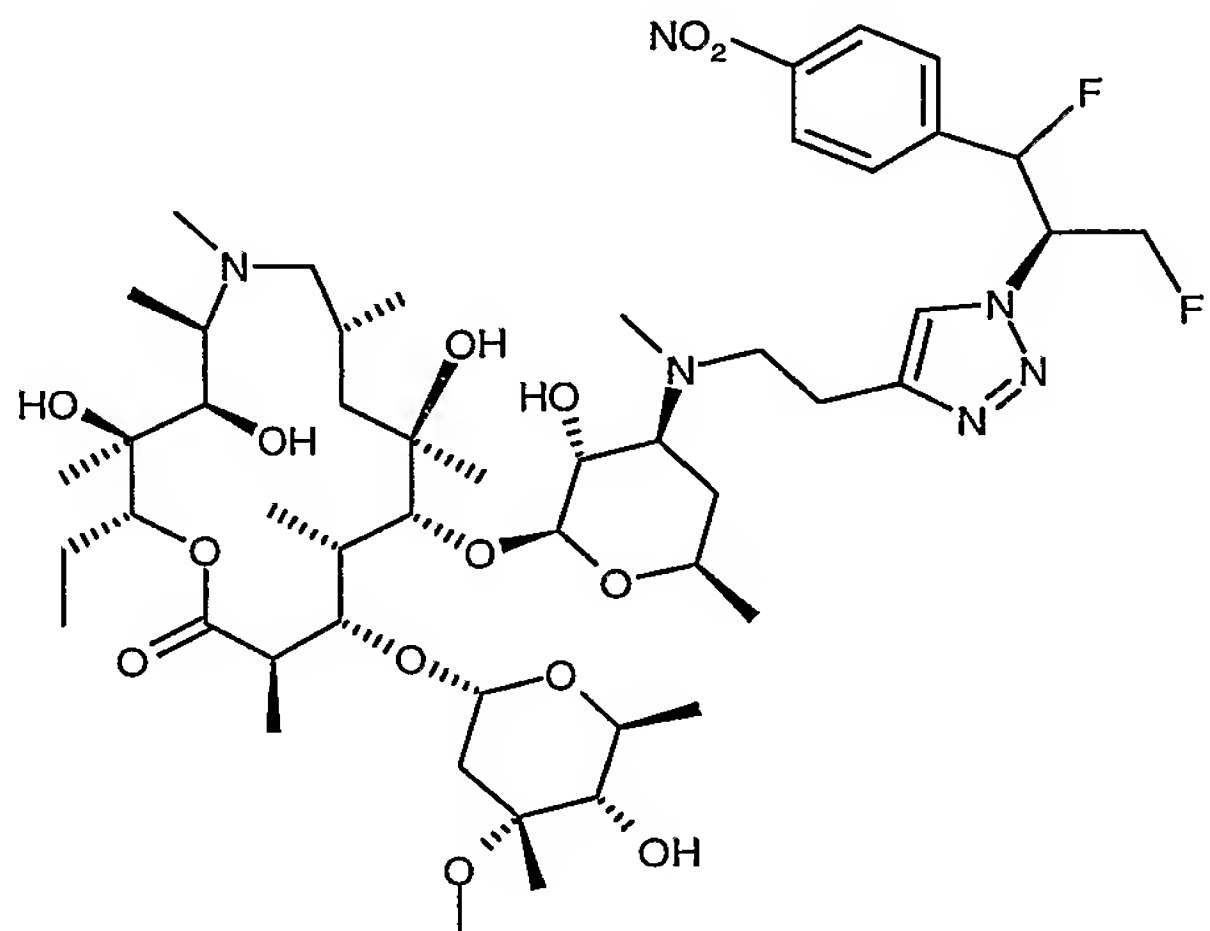
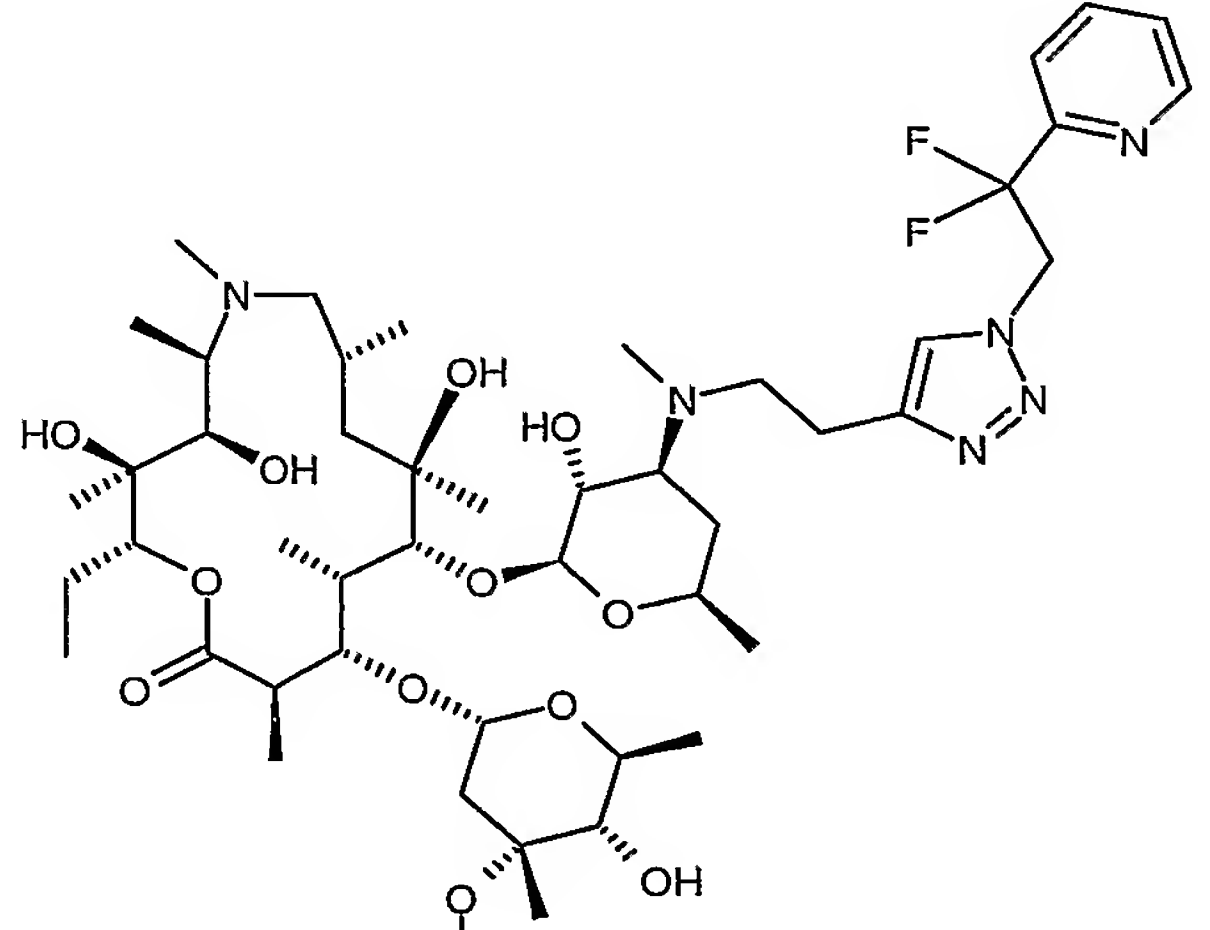
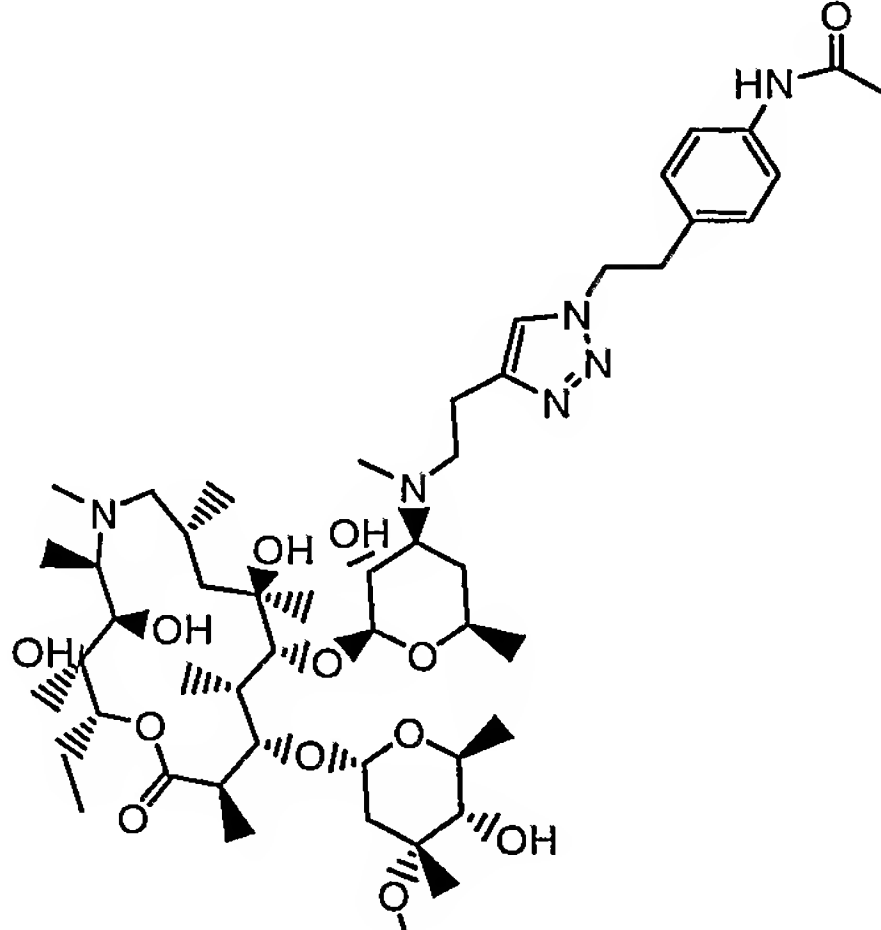
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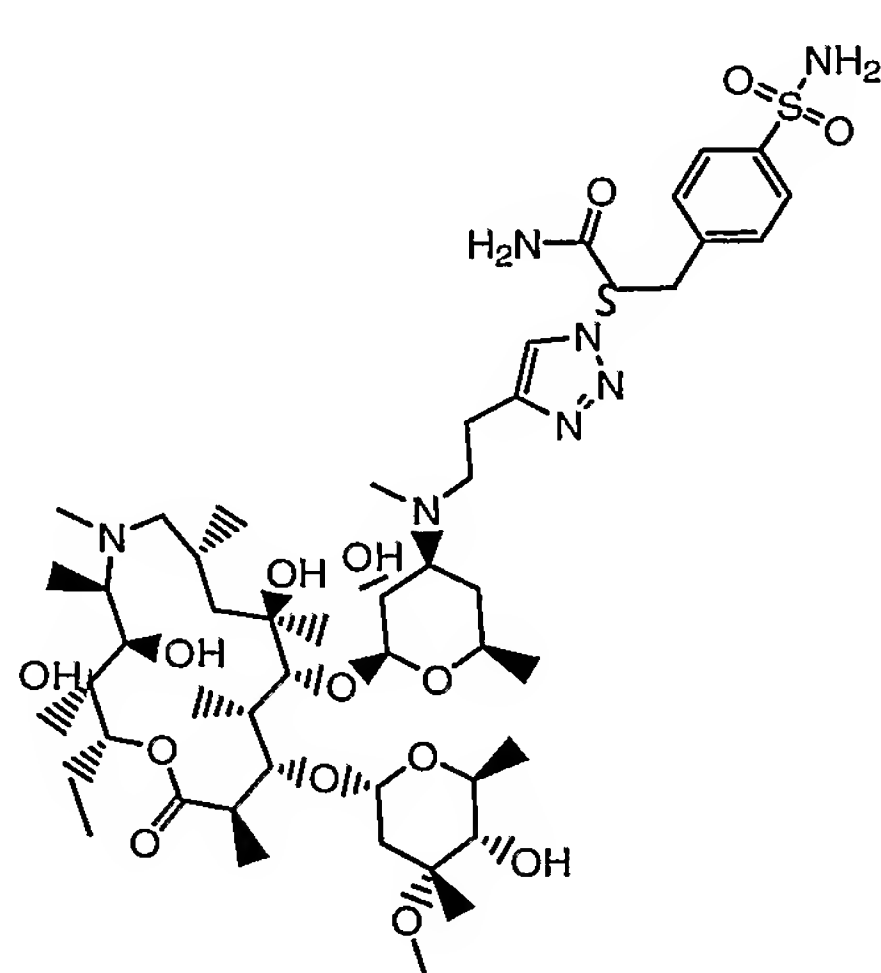
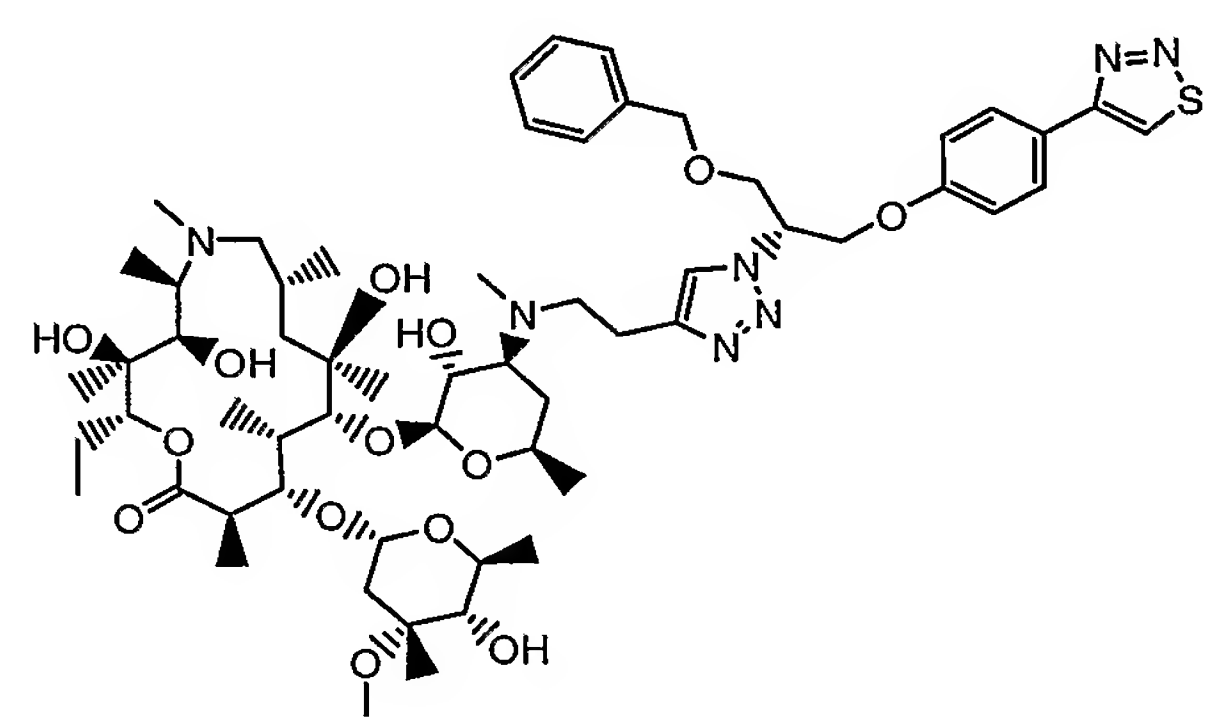
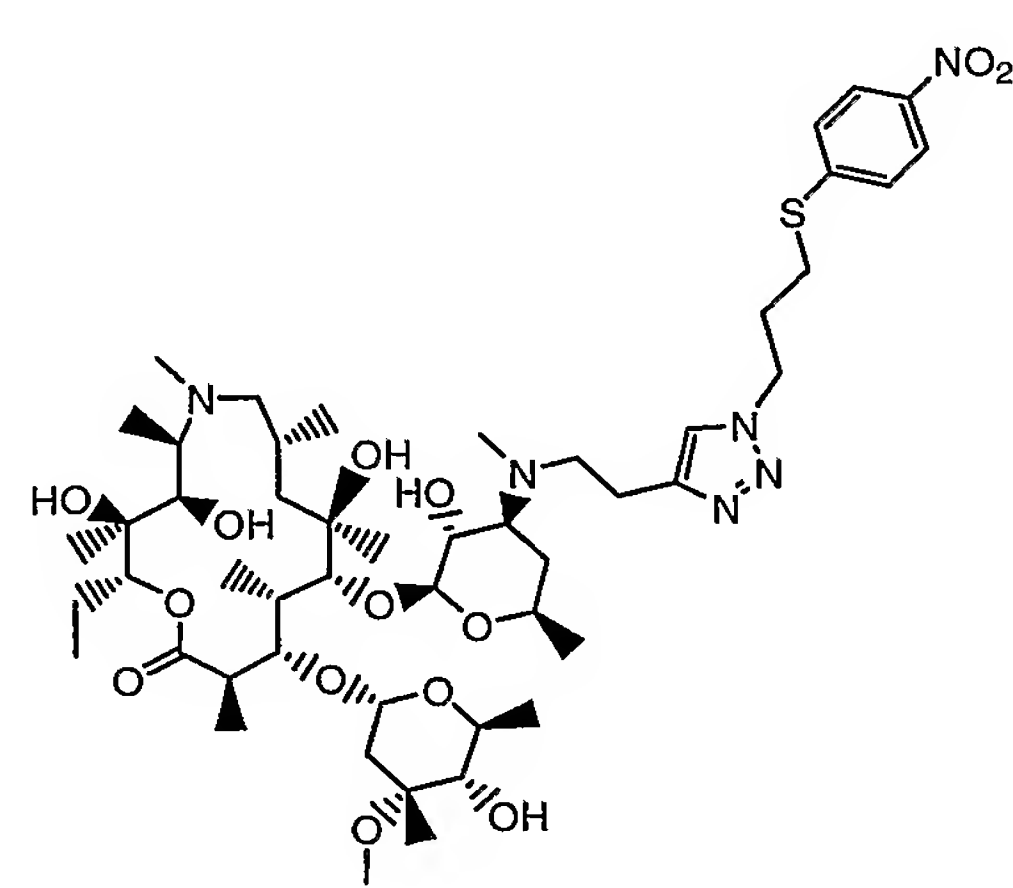


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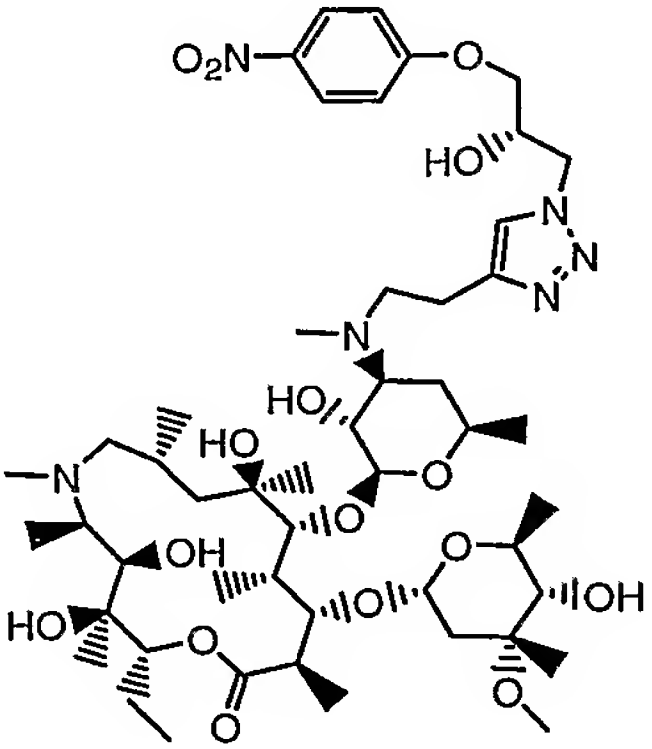
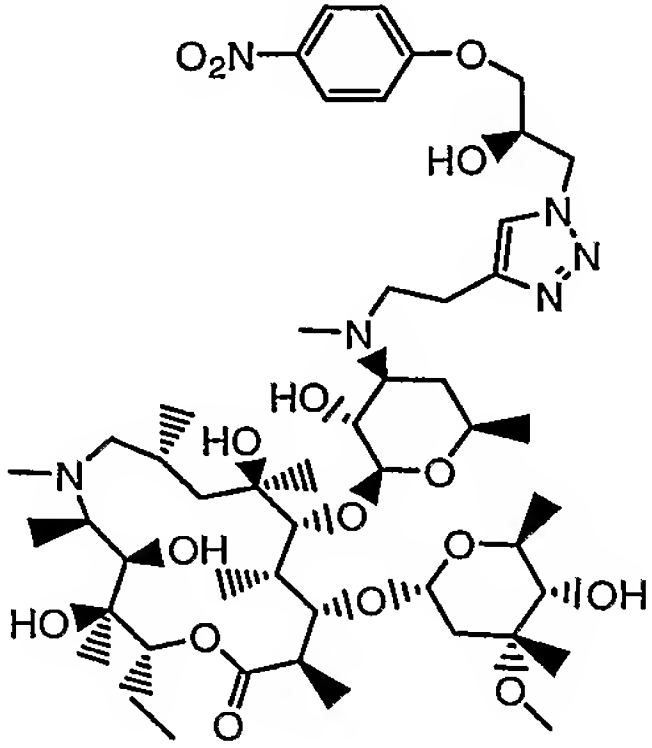
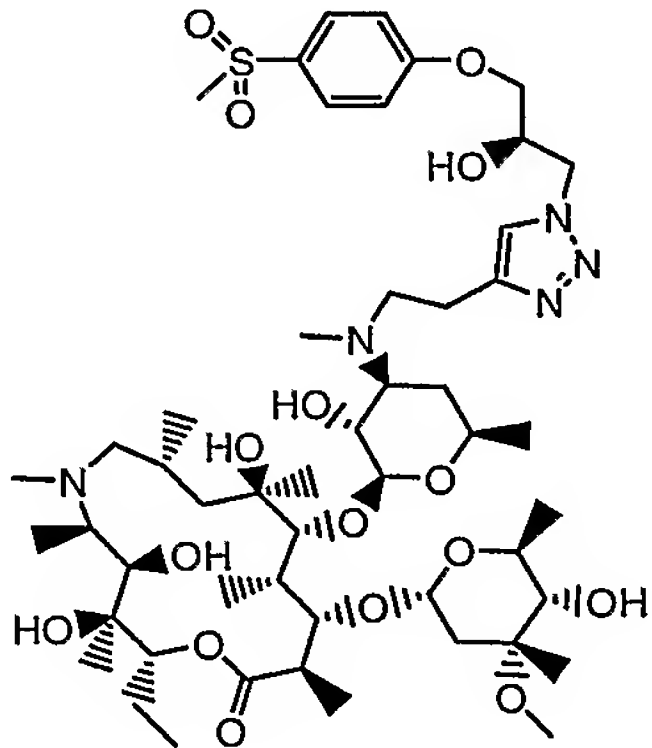


257	 <p>Chemical structure 257: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a methoxy group. It is substituted with a 1,2,4-triazole ring, which is further linked to a 4-nitrophenyl group and a 2-fluoroethyl group.</p>
258	 <p>Chemical structure 258: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a methoxy group. It is substituted with a 1,2,4-triazole ring, which is further linked to a 2-(2-fluoro-2-(pyridin-2-yl)ethyl) group.</p>
259	 <p>Chemical structure 259: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a methoxy group. It is substituted with a 1,2,4-triazole ring, which is further linked to a 4-(acetamido)phenyl group.</p>

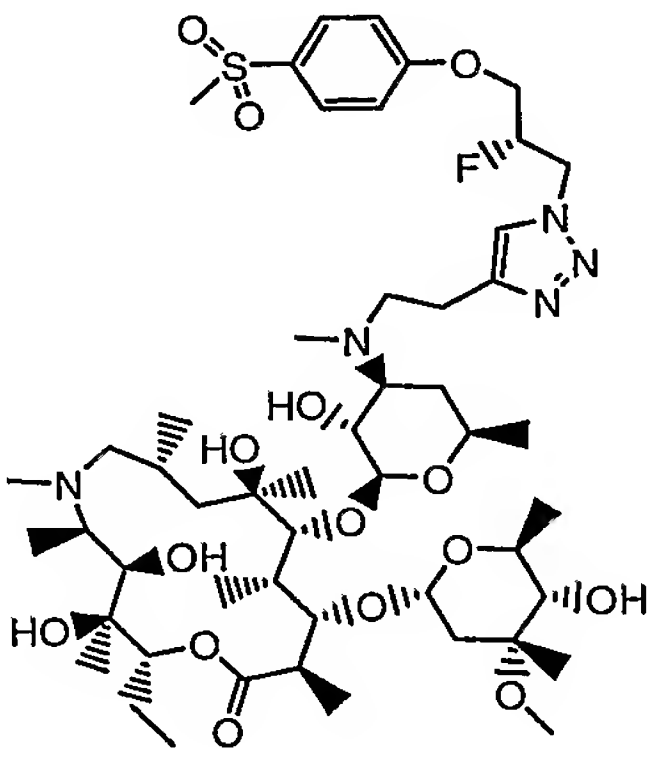
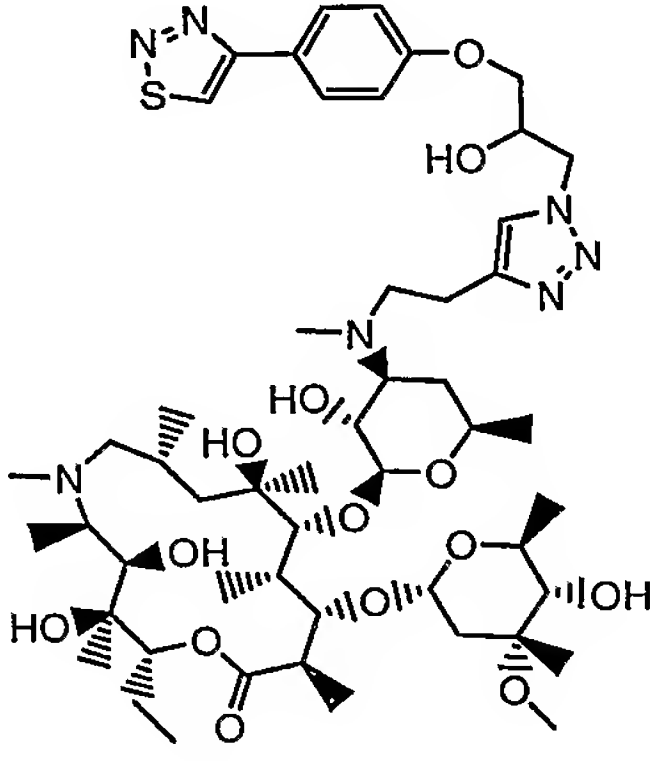
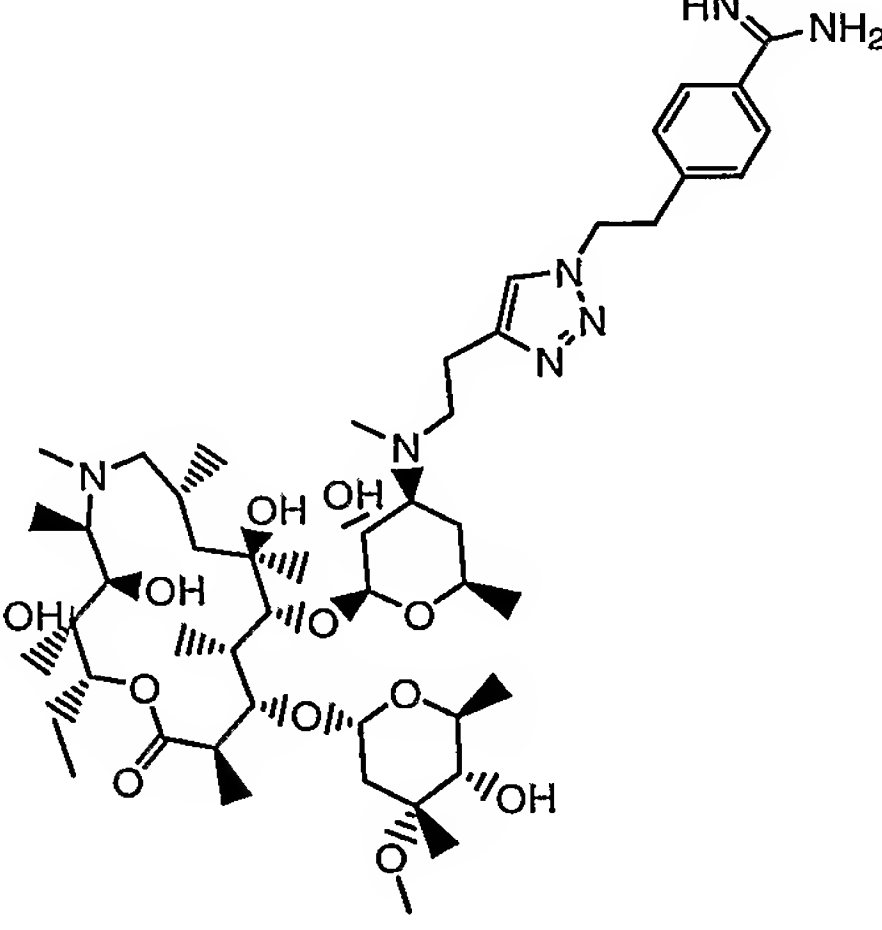
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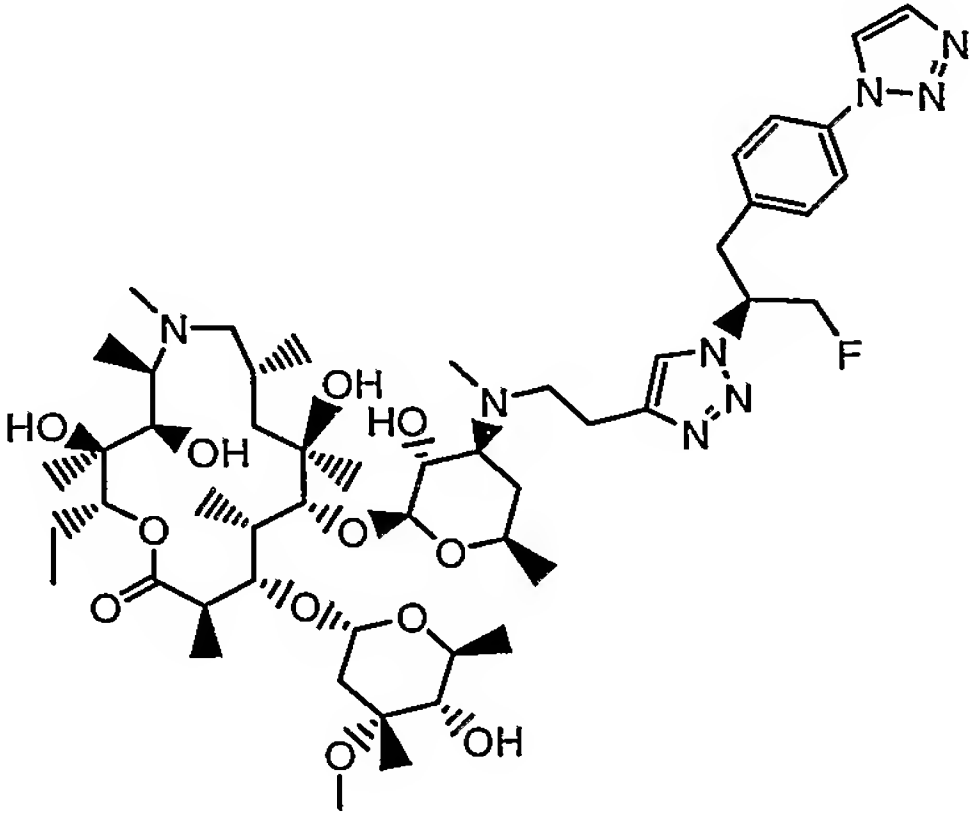
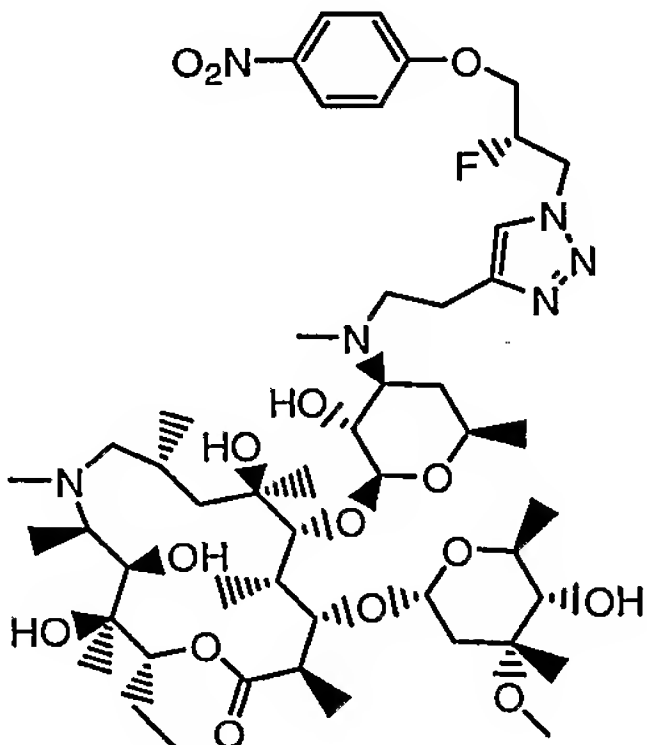
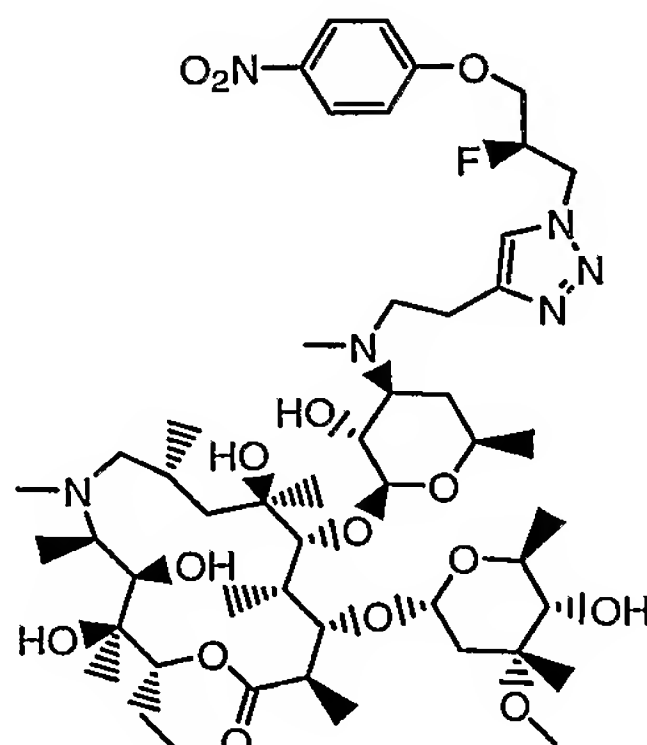
260	 <p>Chemical structure 260 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a sulfonamide group attached via a triazole ring.</p>
261	 <p>Chemical structure 261 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a thioether group attached via a triazole ring.</p>
262	 <p>Chemical structure 262 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a thioether group attached via a triazole ring.</p>

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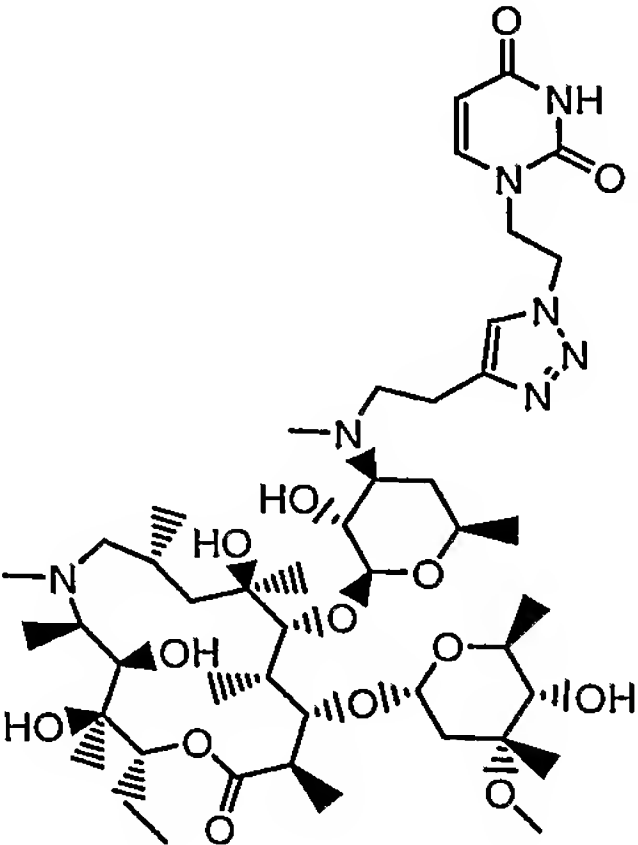
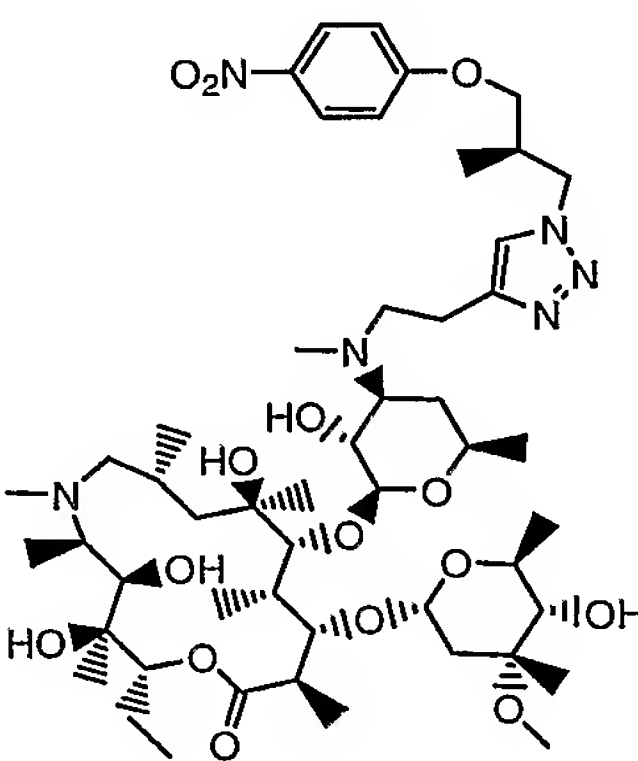
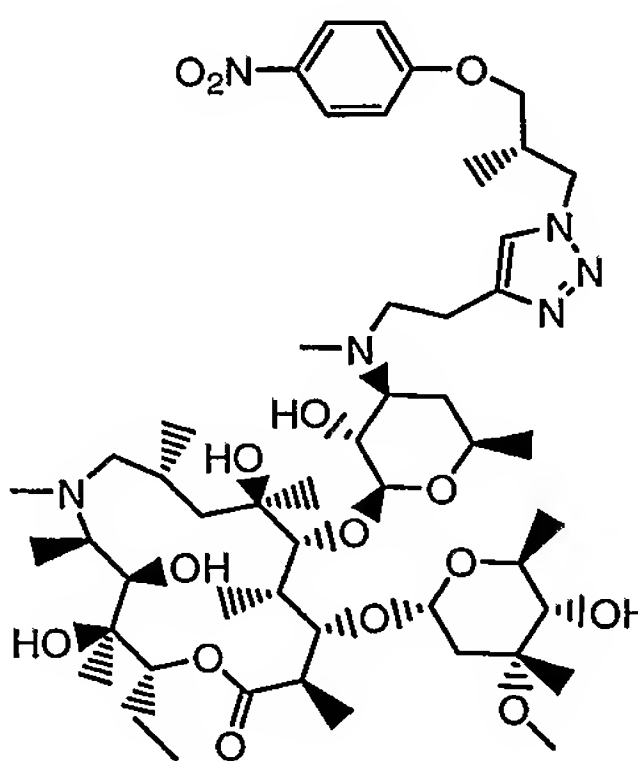
266	 <p>Chemical structure 266 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a side chain containing a 1,2,3-triazole ring and a 4-nitrophenyl group.</p>
267	 <p>Chemical structure 267 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a side chain containing a 1,2,3-triazole ring and a 4-nitrophenyl group.</p>
268	 <p>Chemical structure 268 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a side chain containing a 1,2,3-triazole ring and a 4-sulfonylphenyl group.</p>

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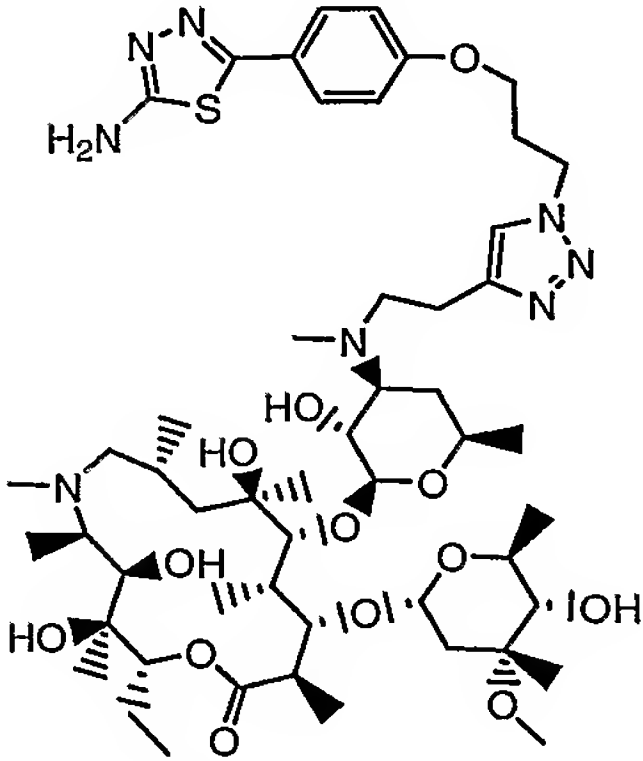
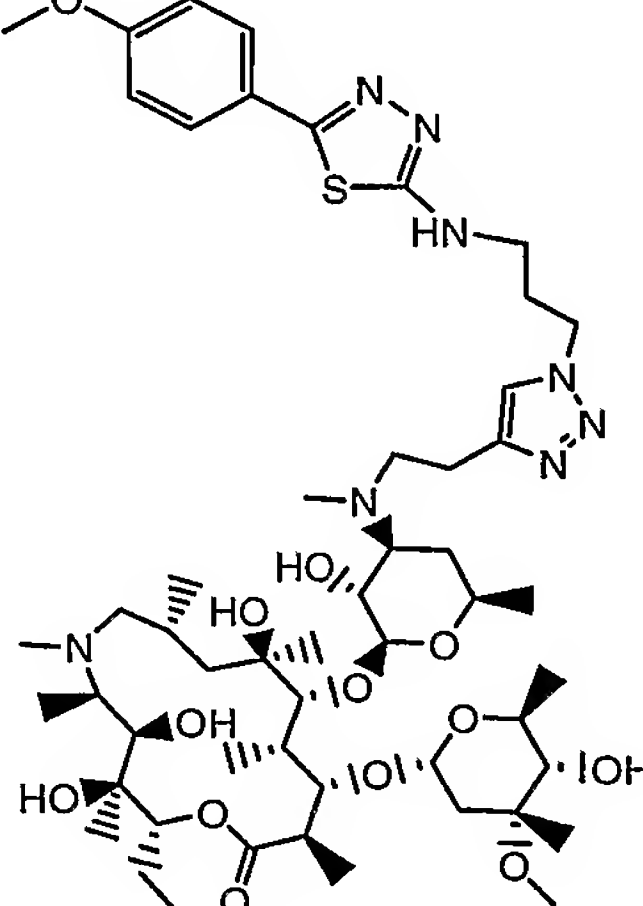
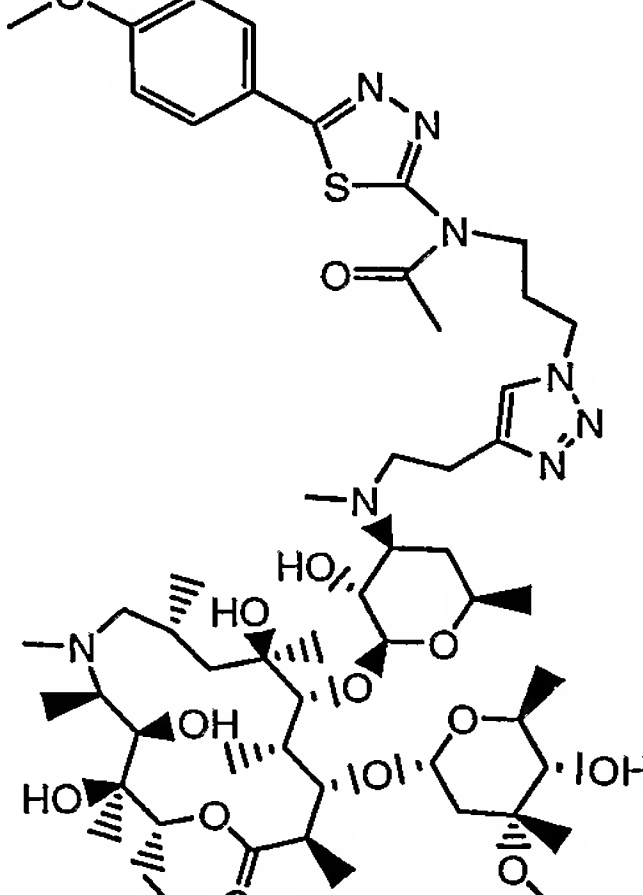
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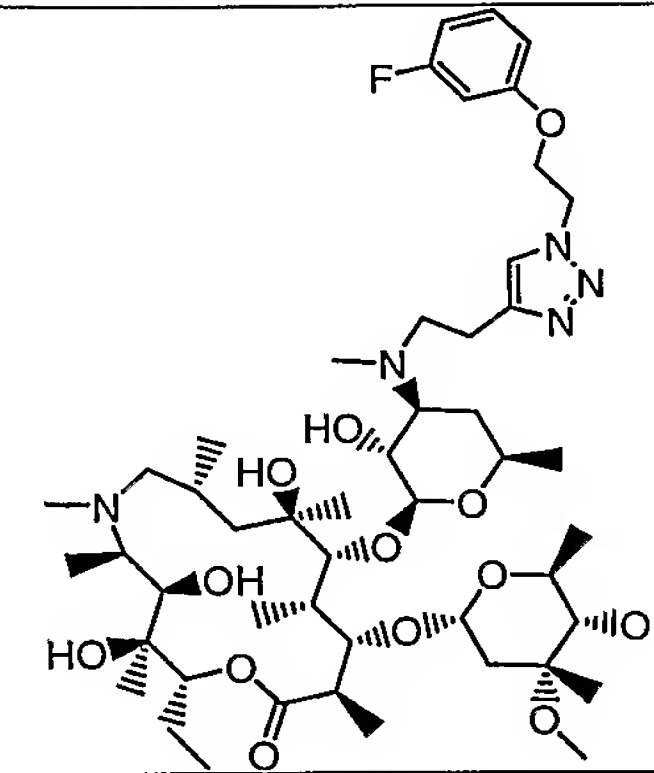
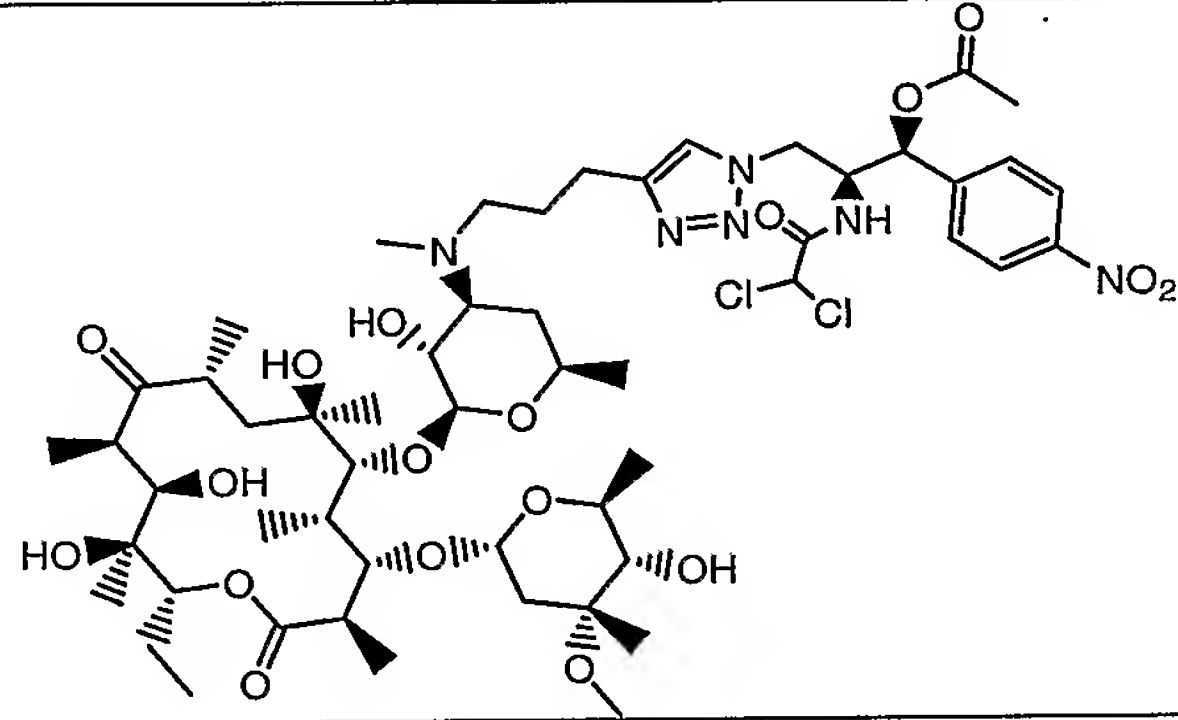
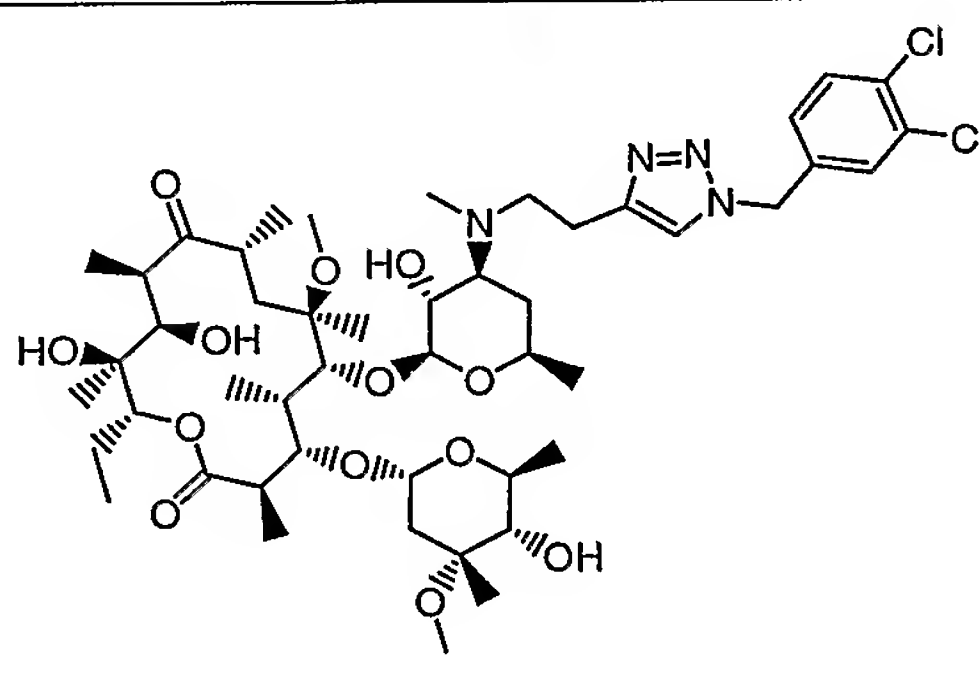
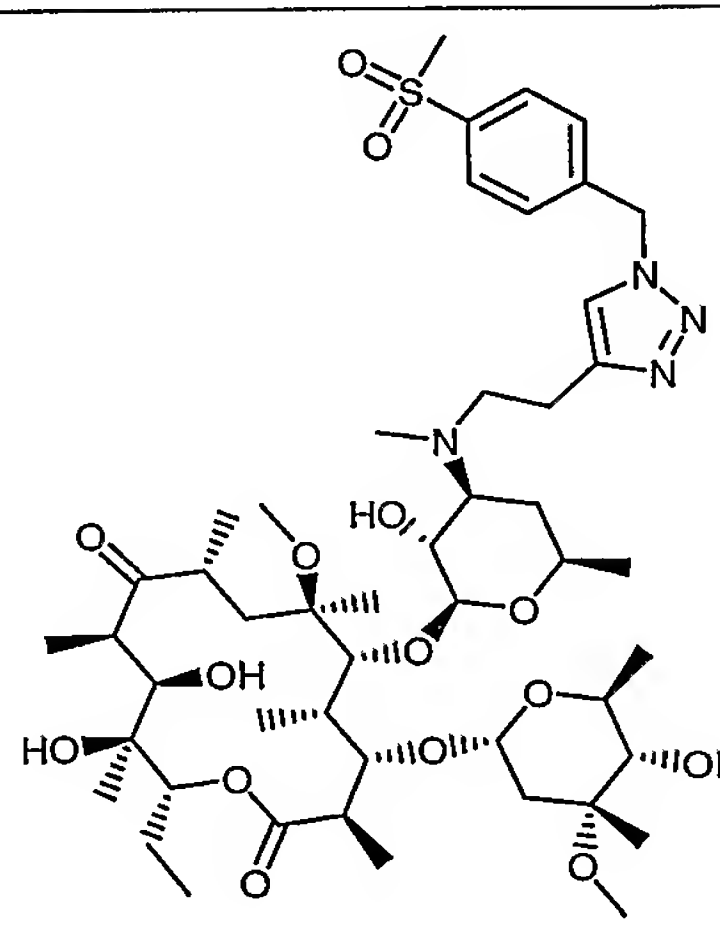
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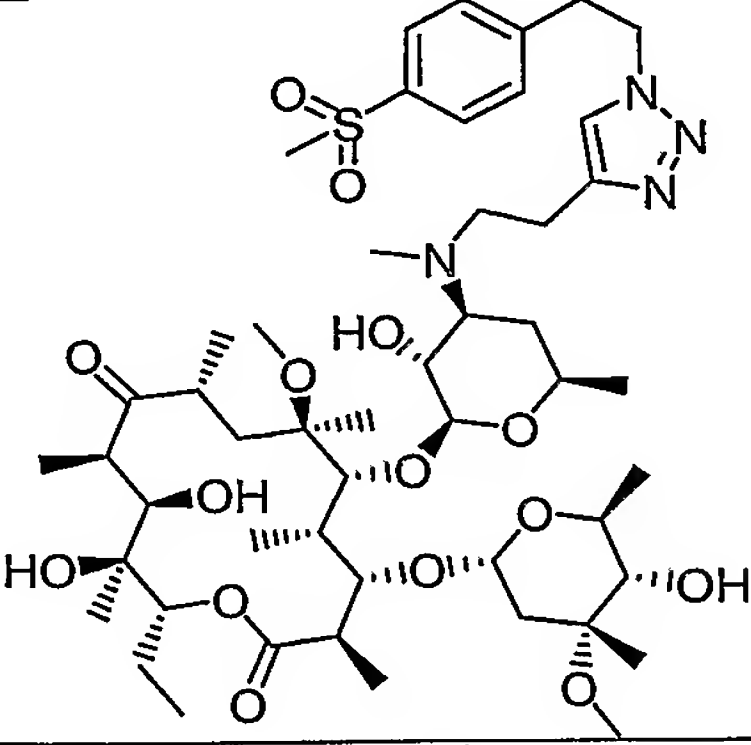
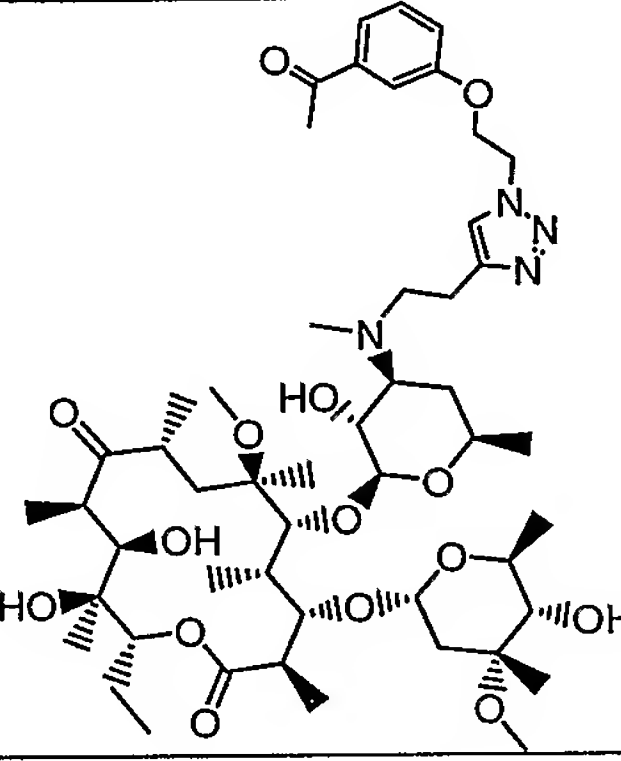
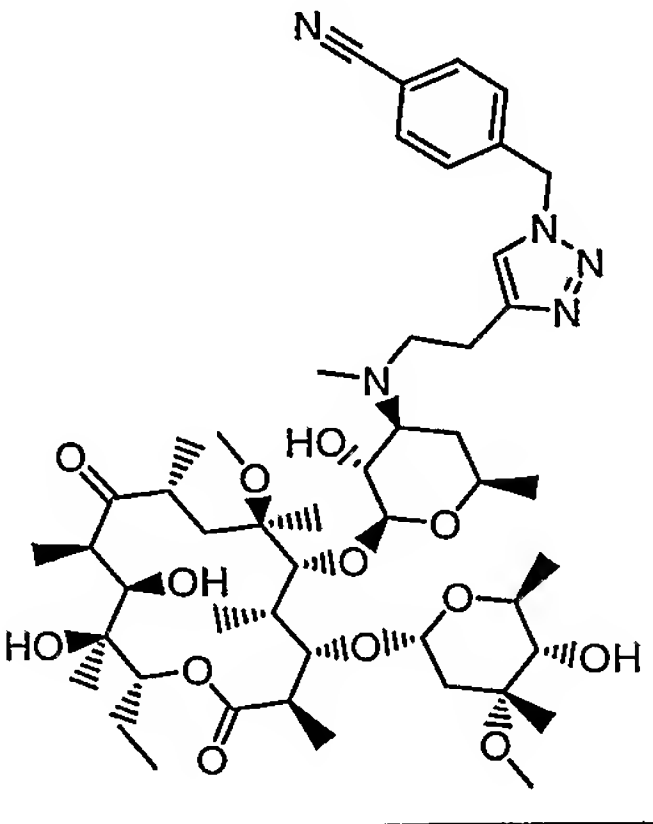
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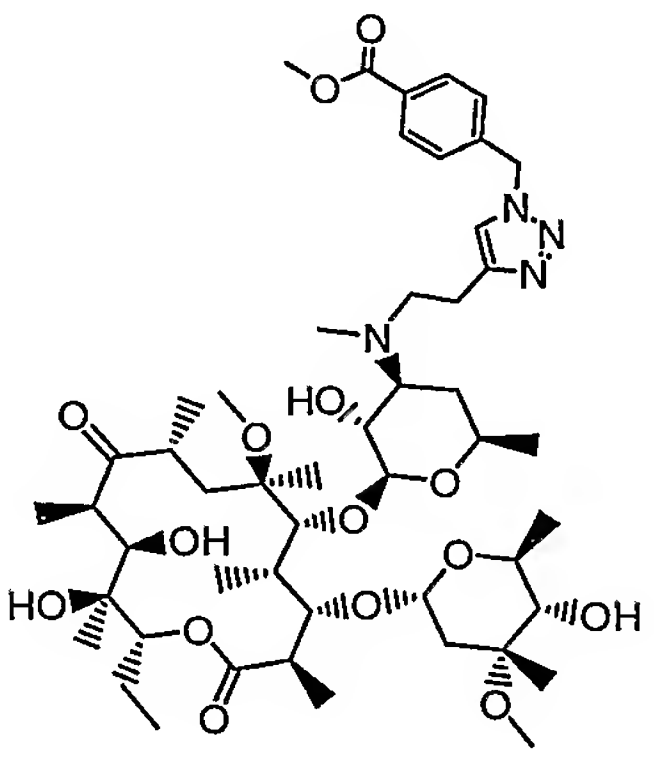
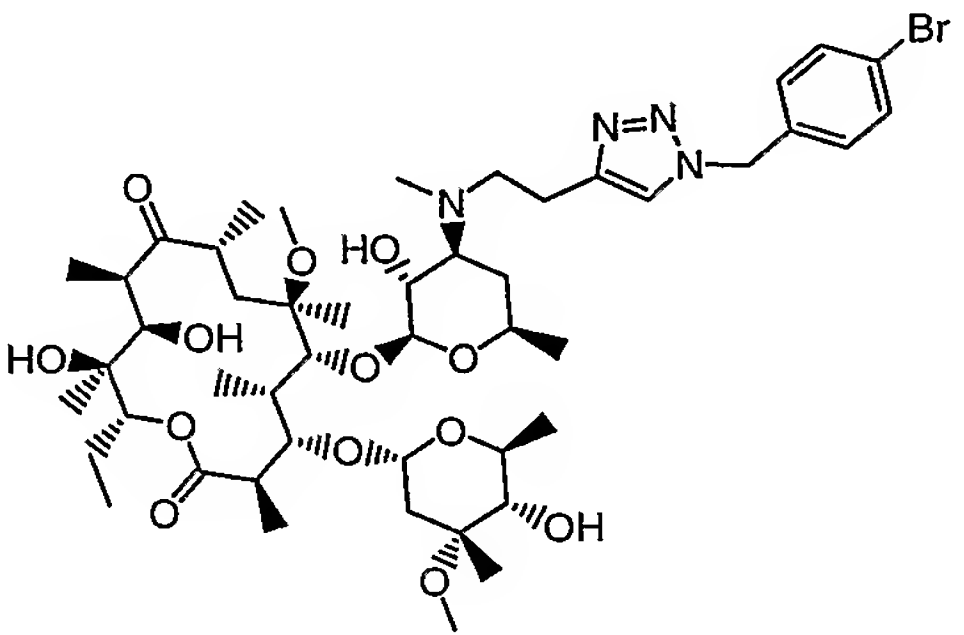
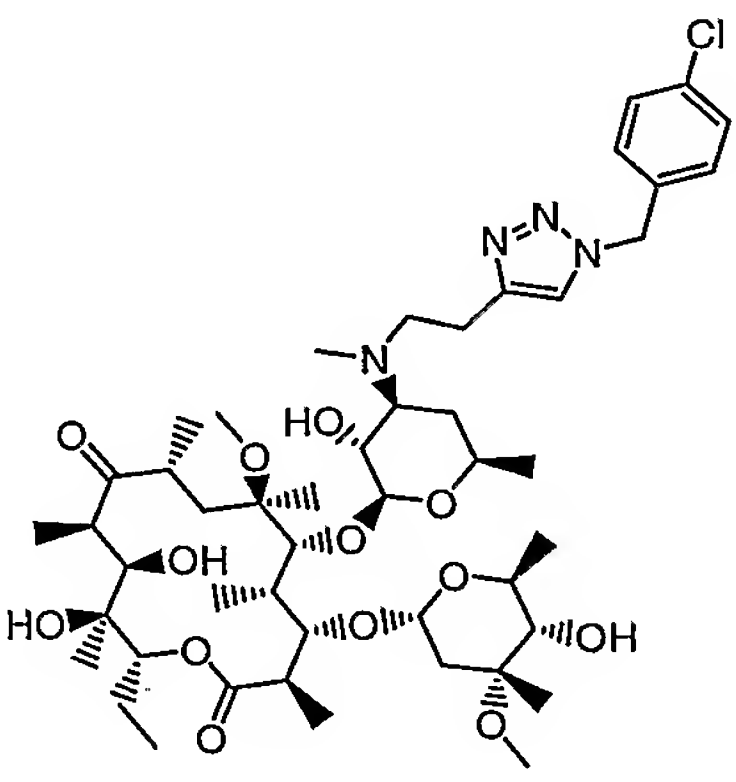
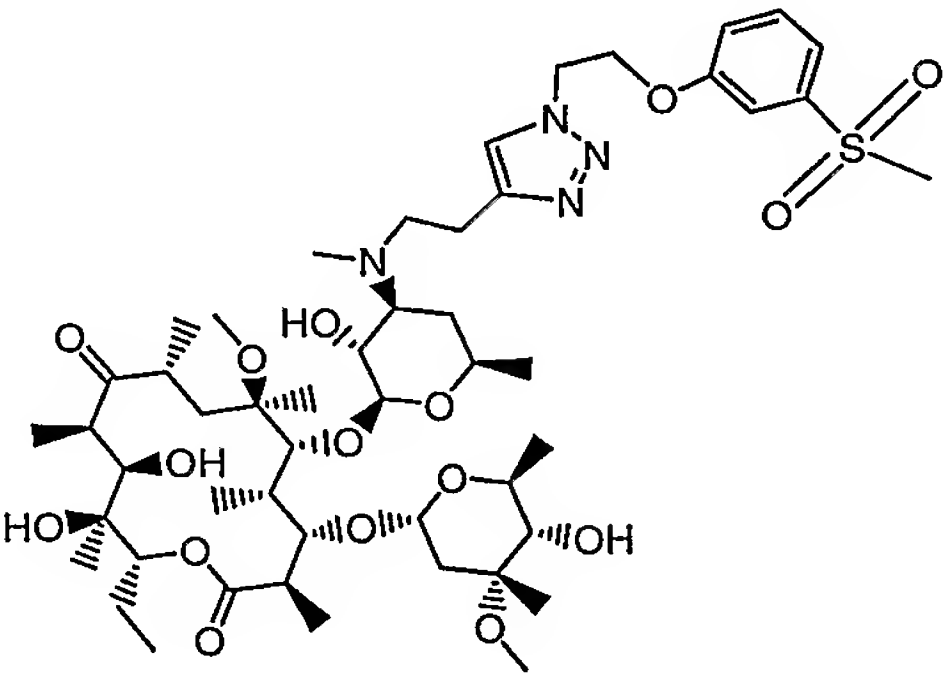
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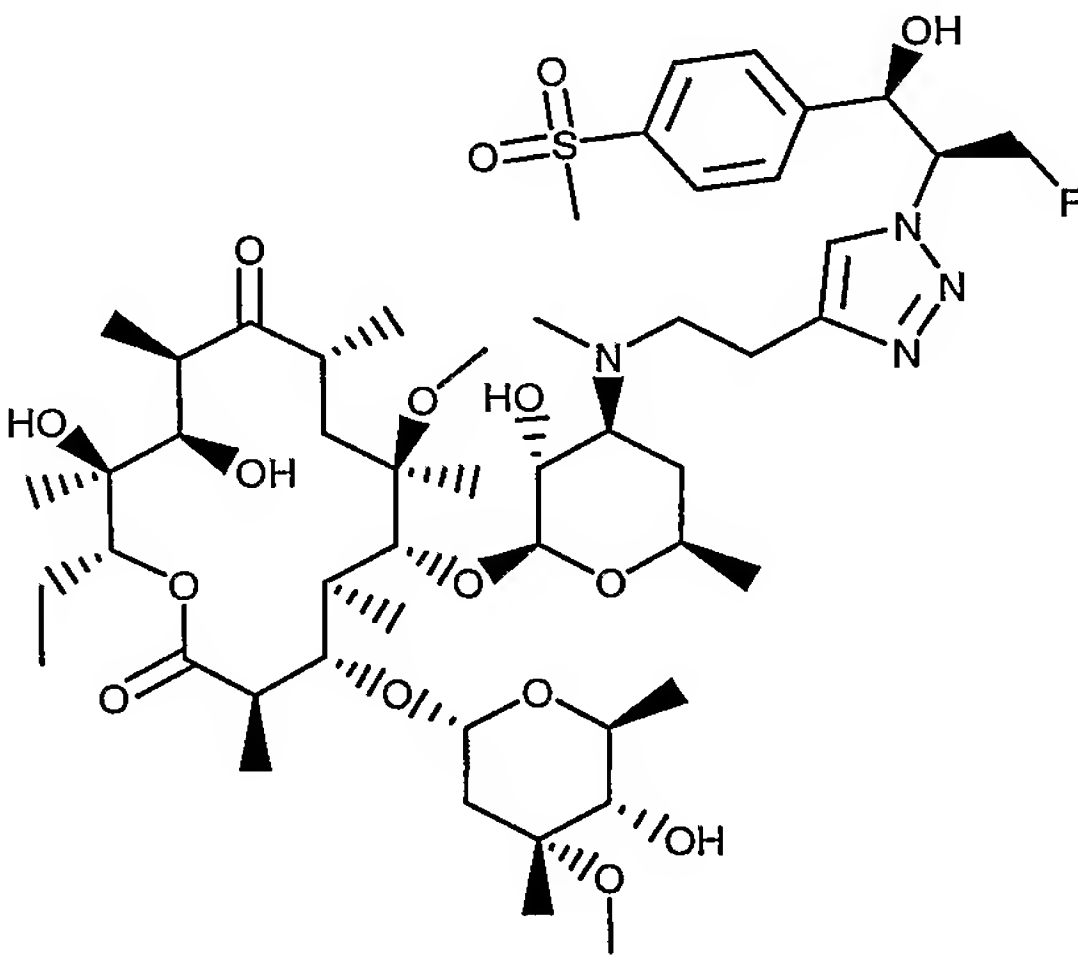
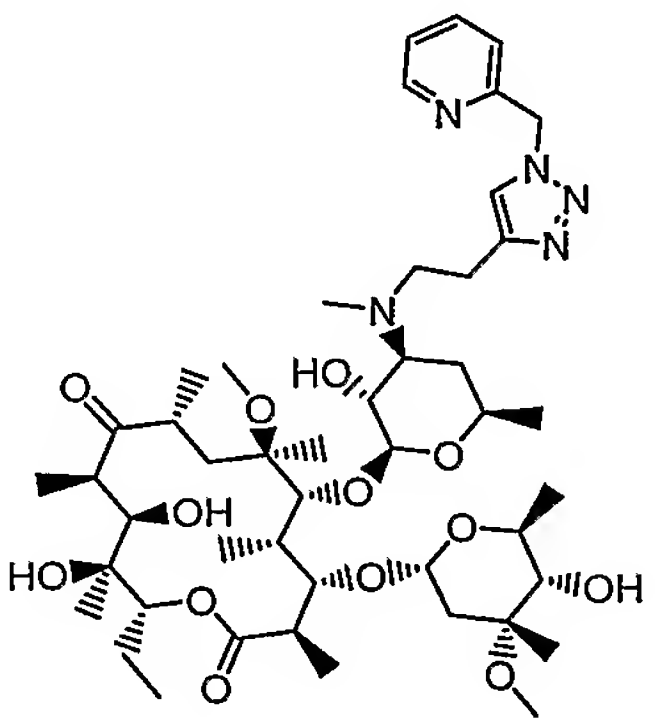
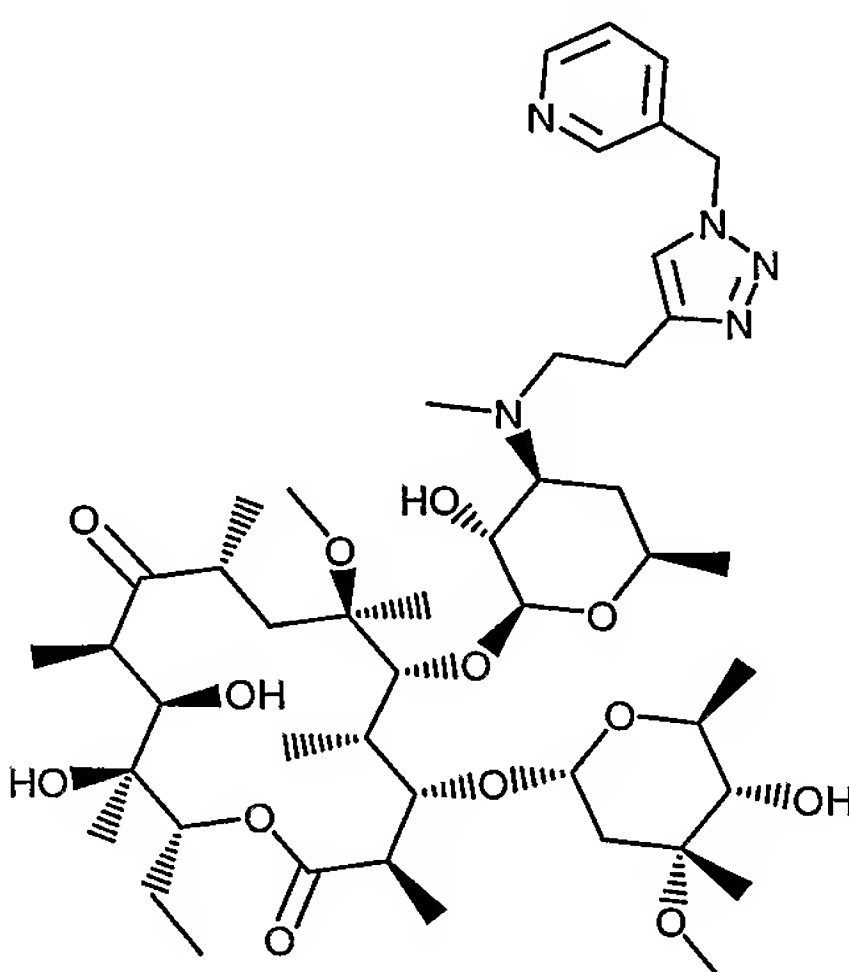
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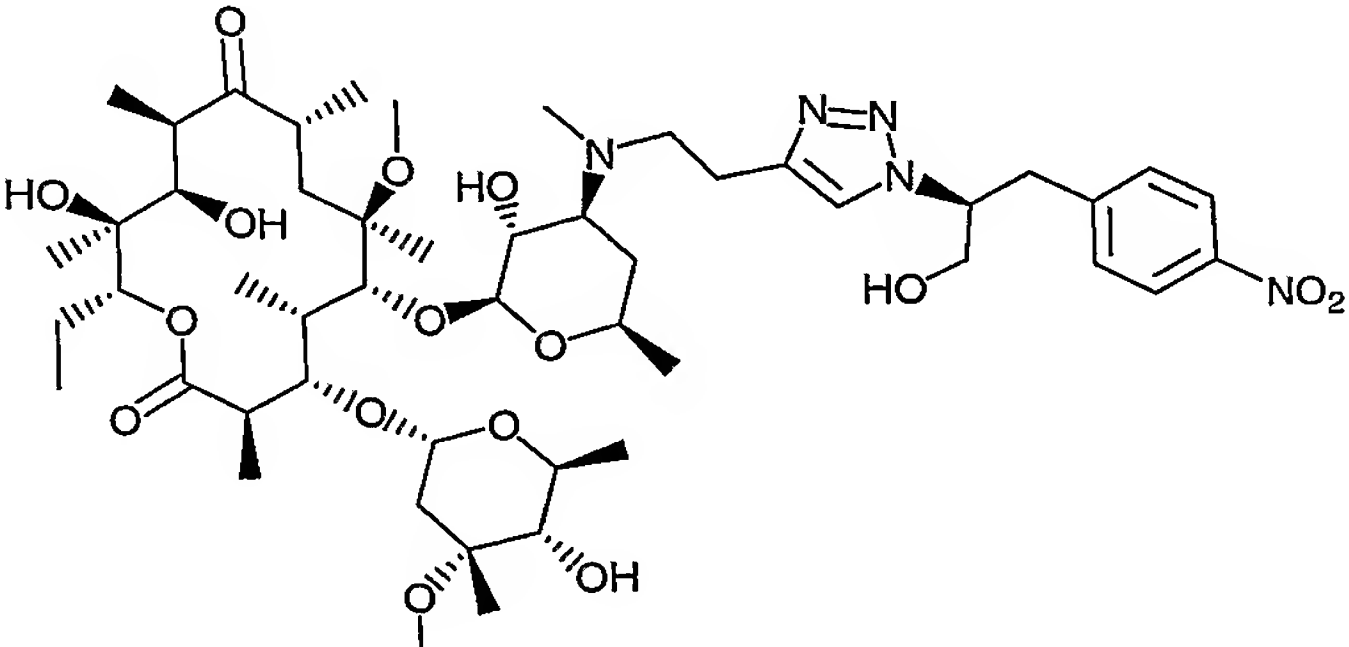
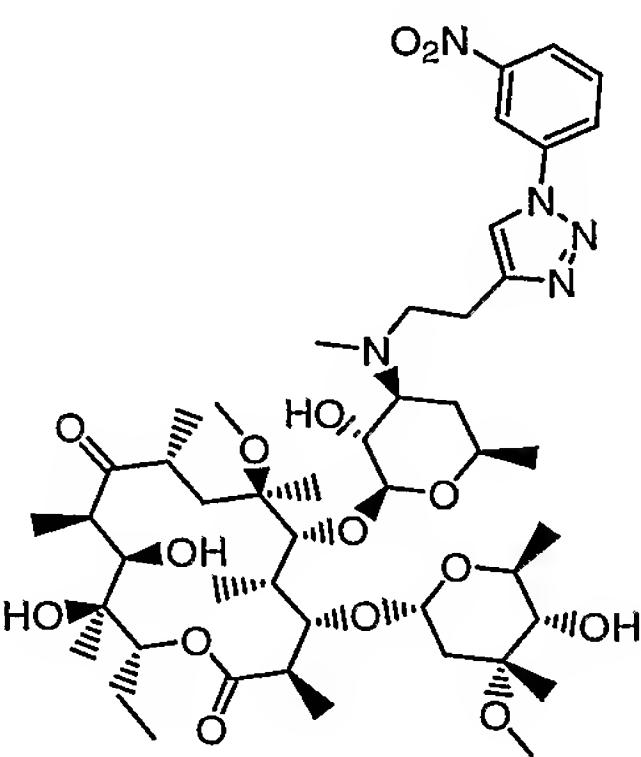
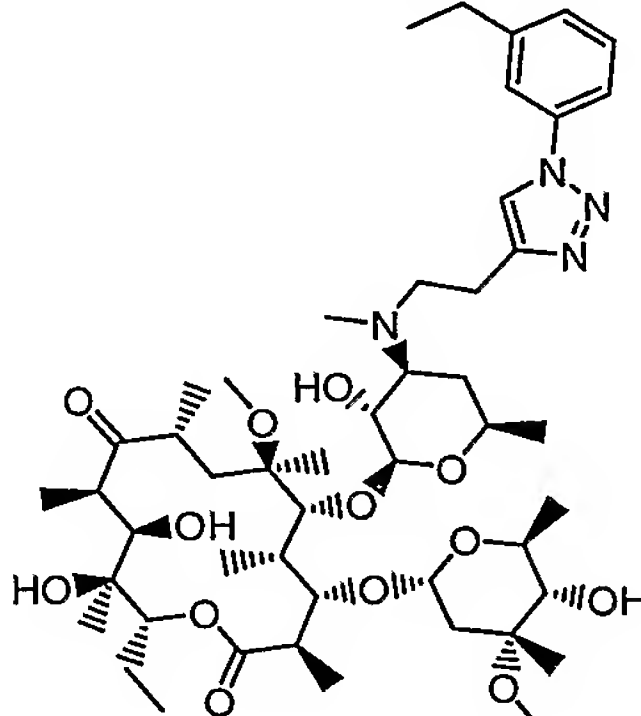
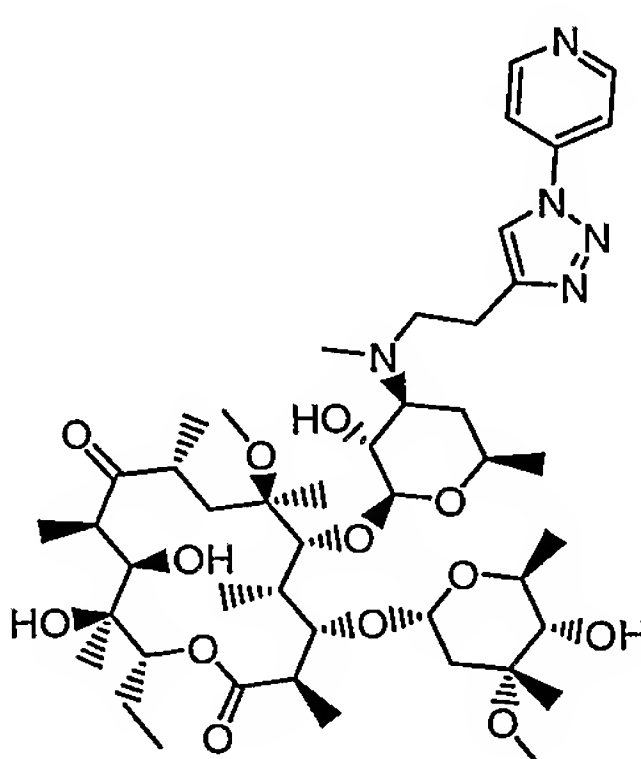
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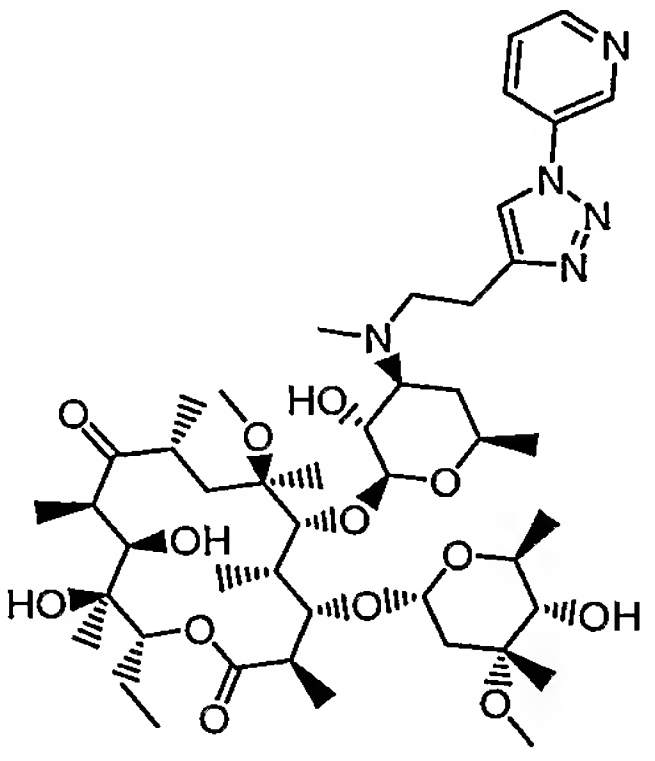
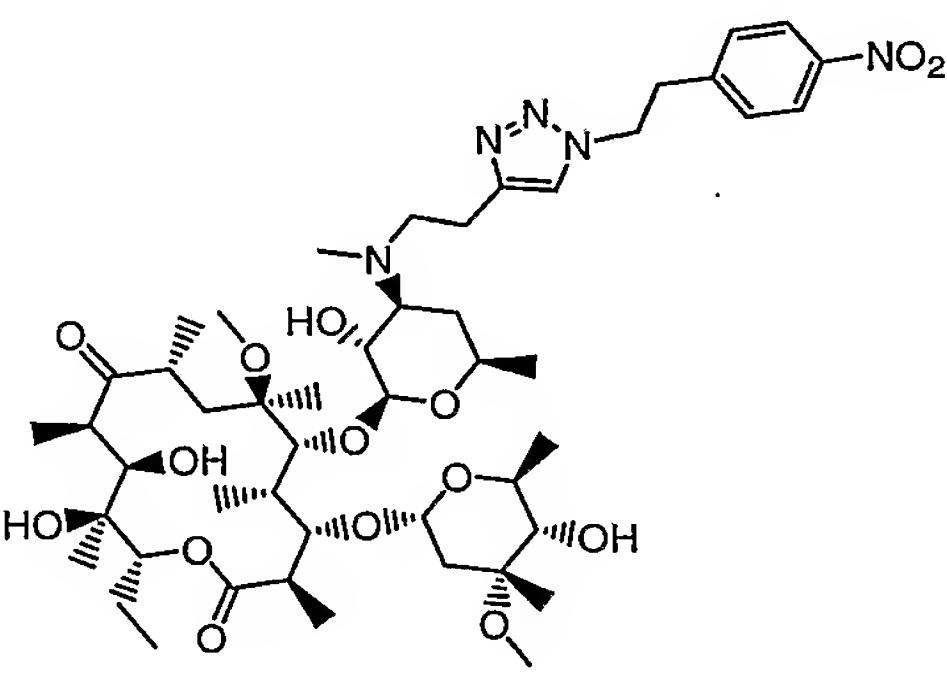
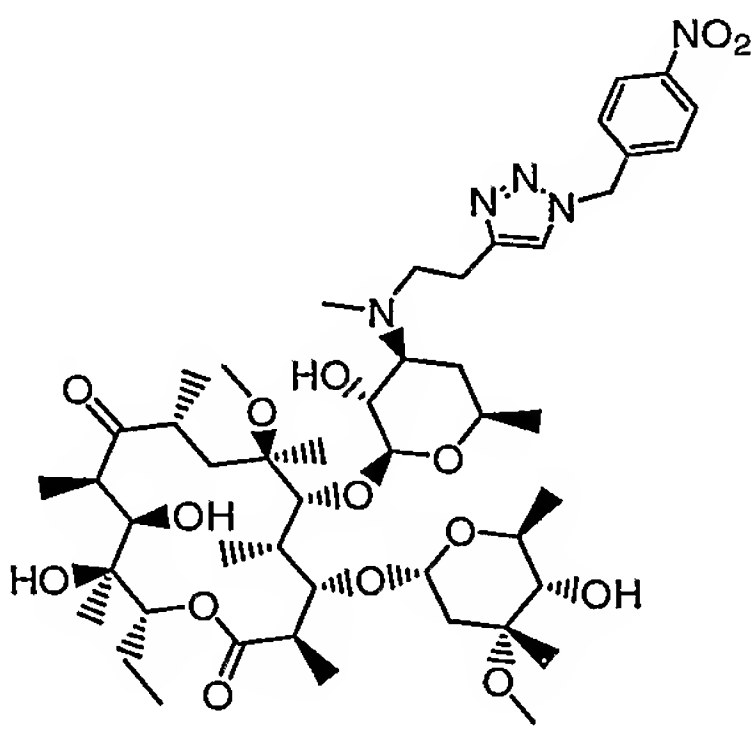
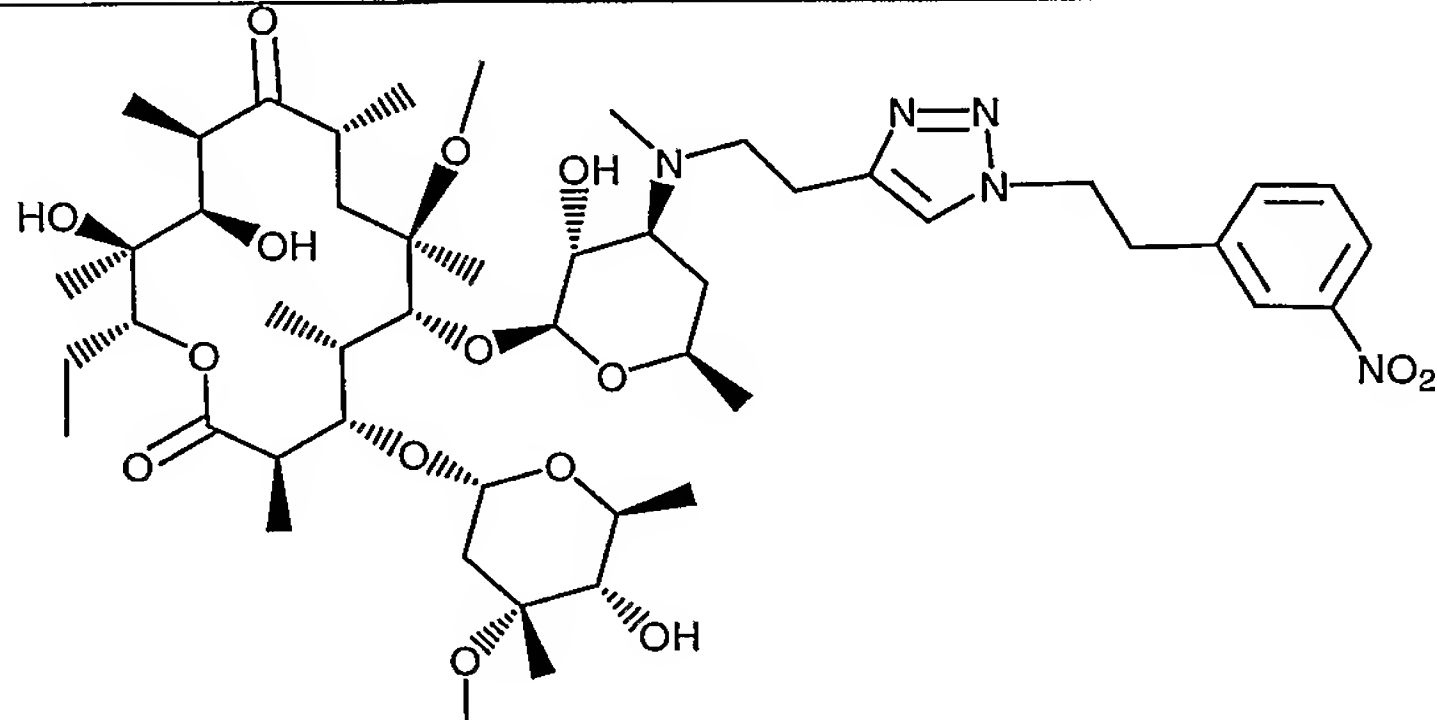
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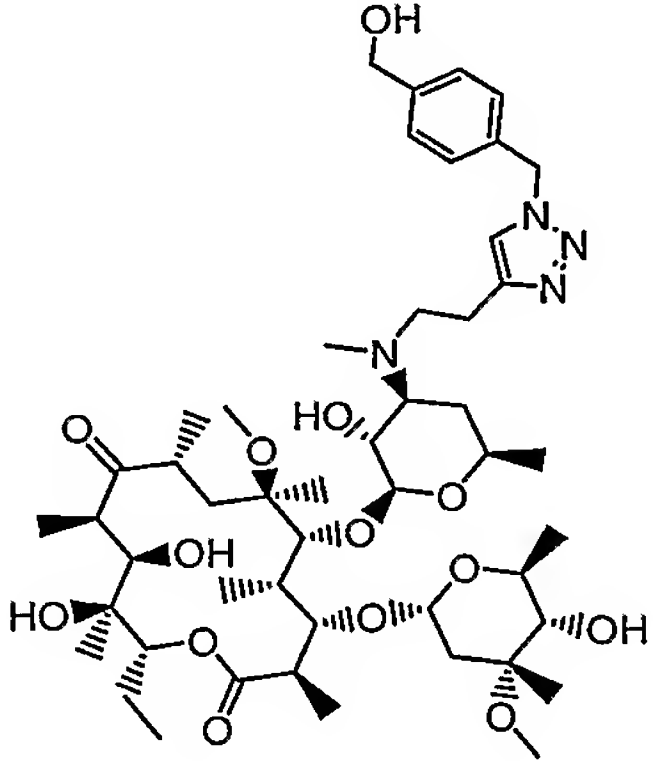
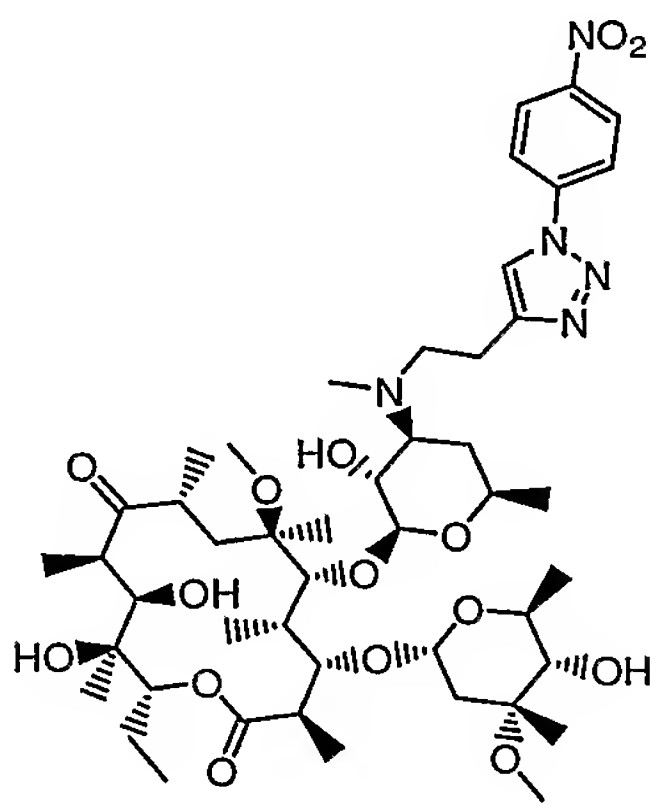
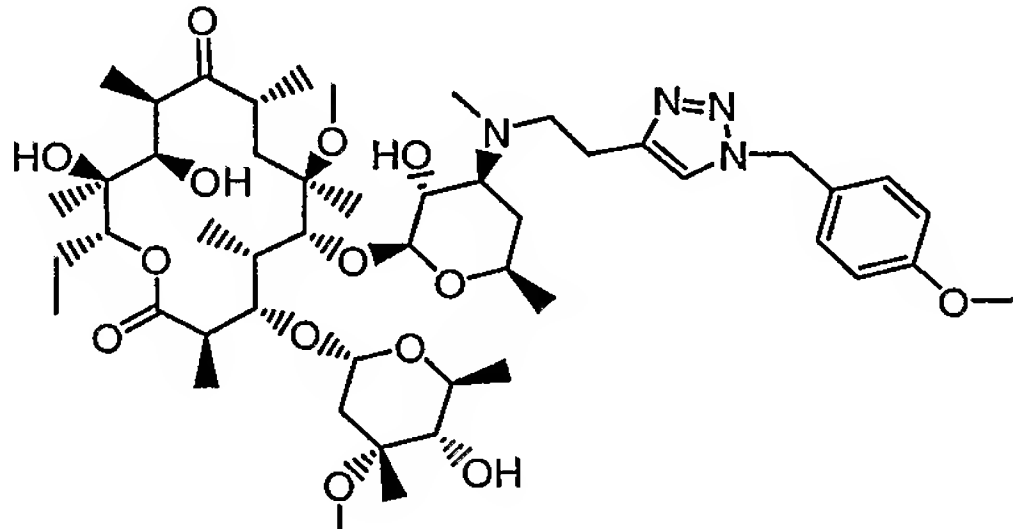
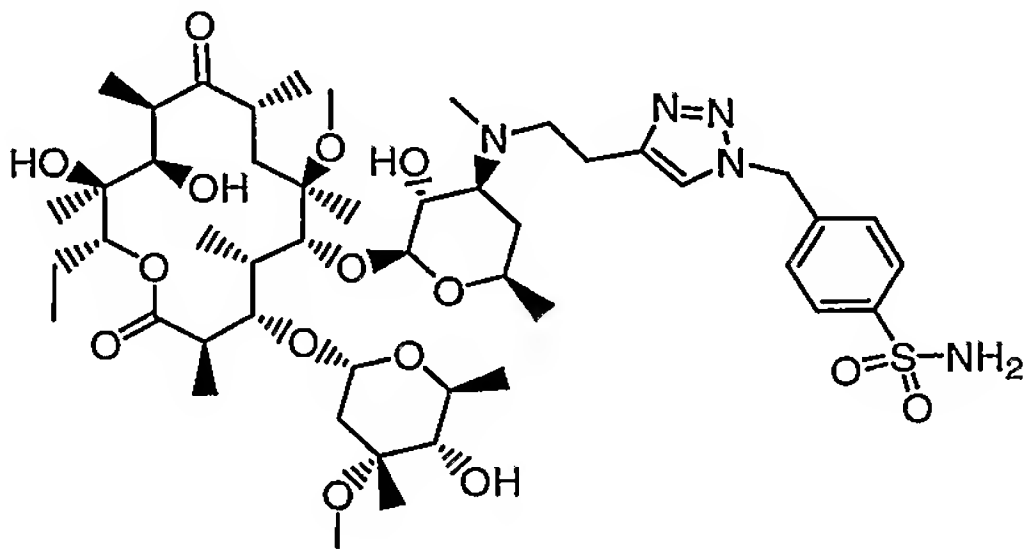
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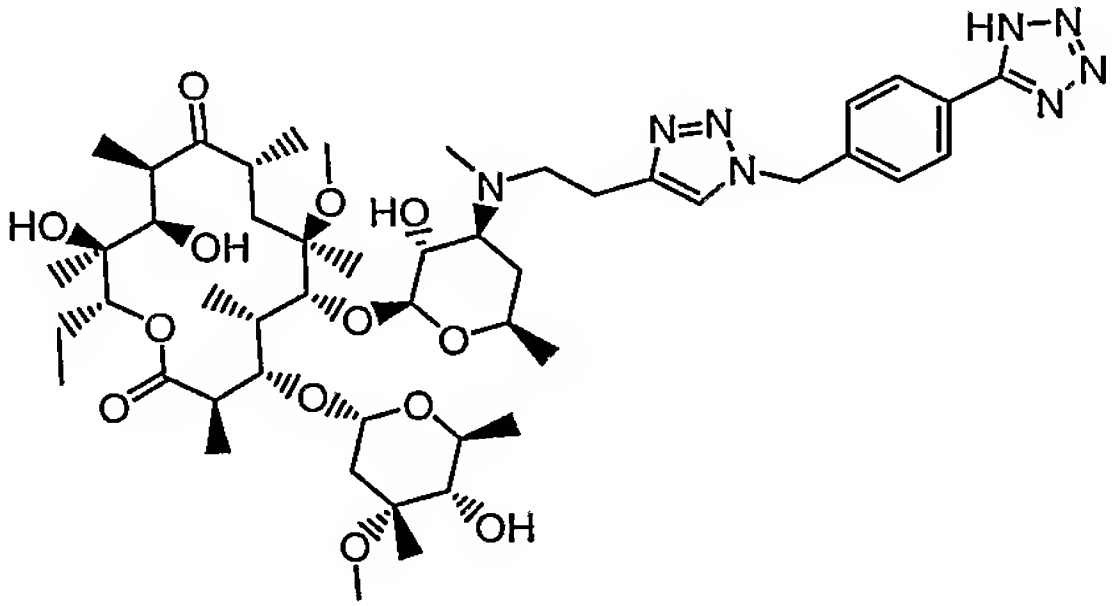
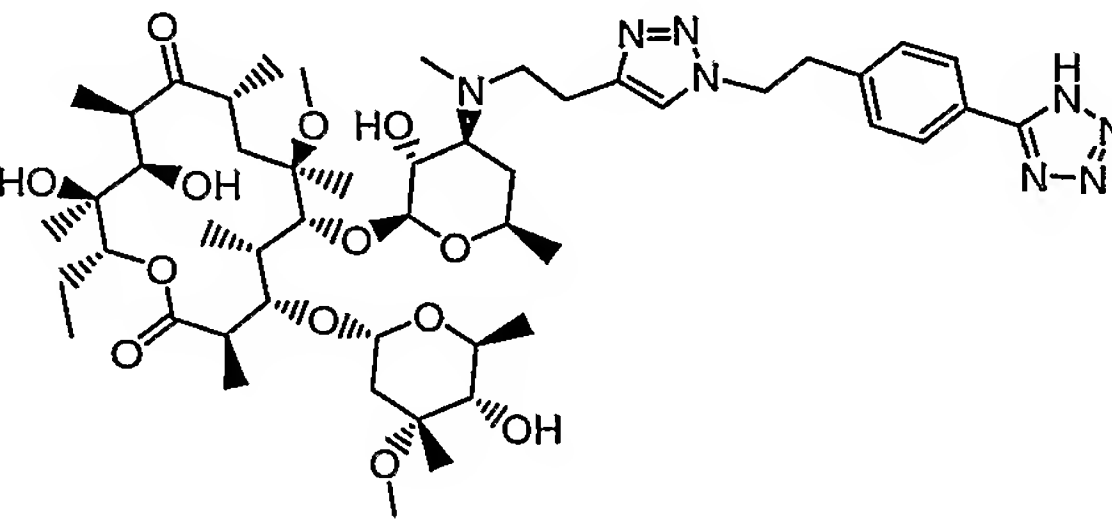
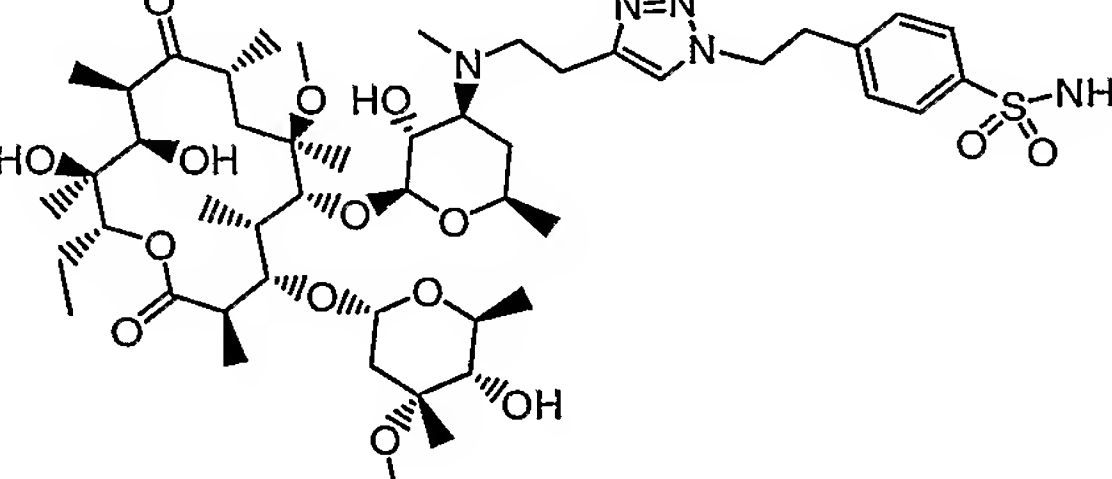
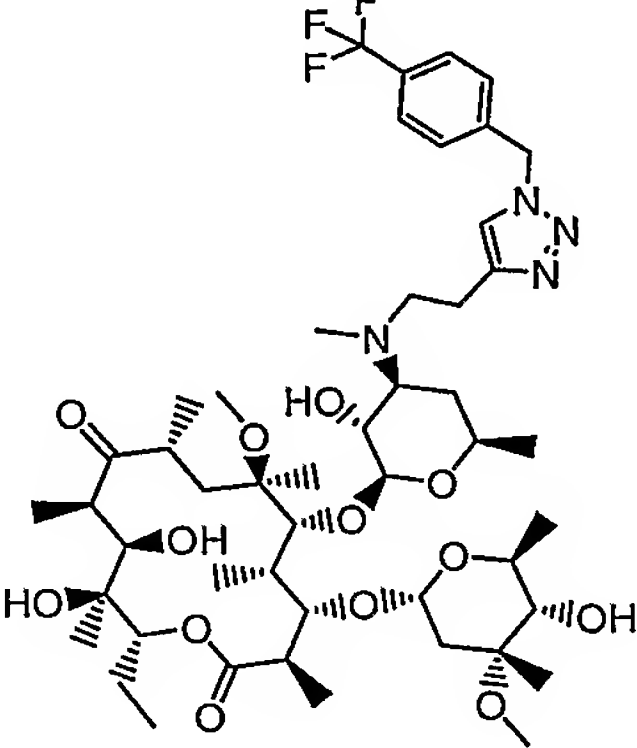
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318	 <p>Chemical structure 318 is a complex polycyclic molecule. It features a central core with multiple hydroxyl groups and a pyridine ring connected via a triazole linker.</p>
319	 <p>Chemical structure 319 is a complex polycyclic molecule. It features a central core with multiple hydroxyl groups and a nitrophenyl ring connected via a triazole linker.</p>
320	 <p>Chemical structure 320 is a complex polycyclic molecule. It features a central core with multiple hydroxyl groups and a nitrophenyl ring connected via a triazole linker.</p>
321	 <p>Chemical structure 321 is a complex polycyclic molecule. It features a central core with multiple hydroxyl groups and a nitrophenyl ring connected via a triazole linker.</p>

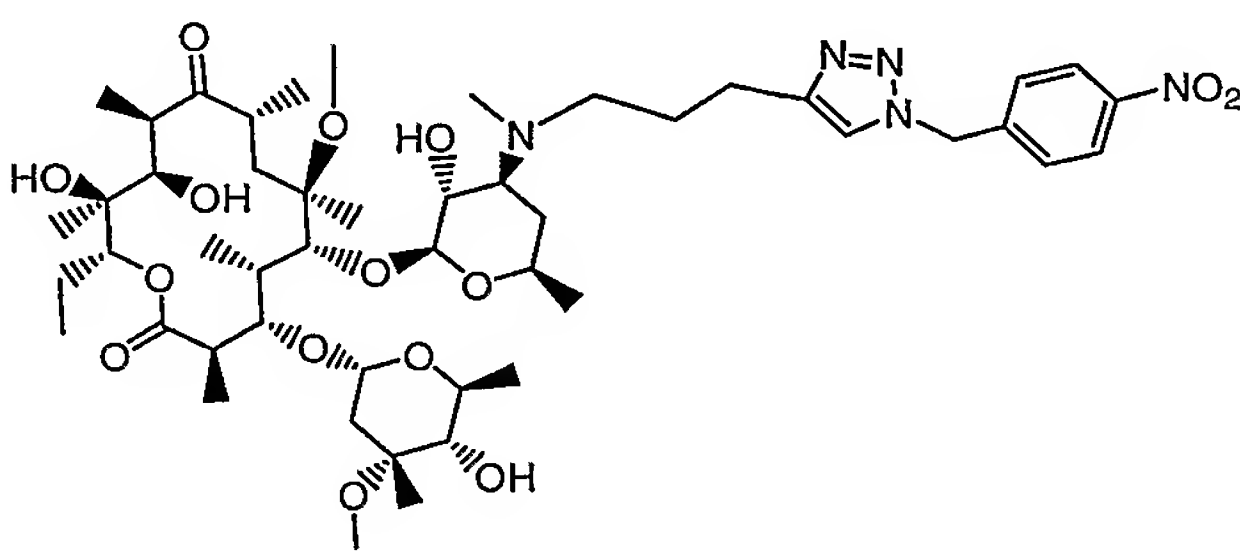
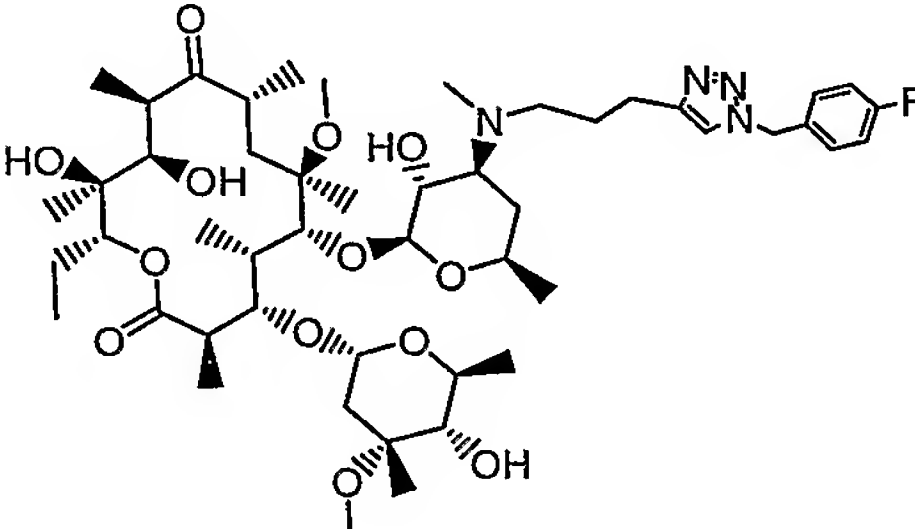
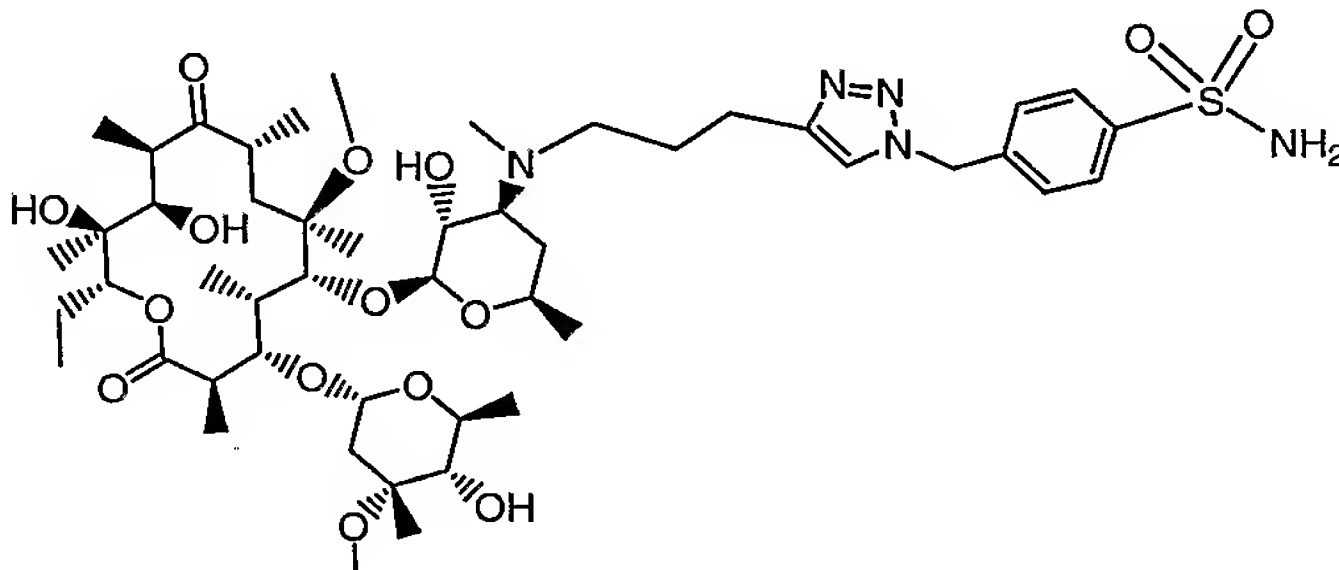
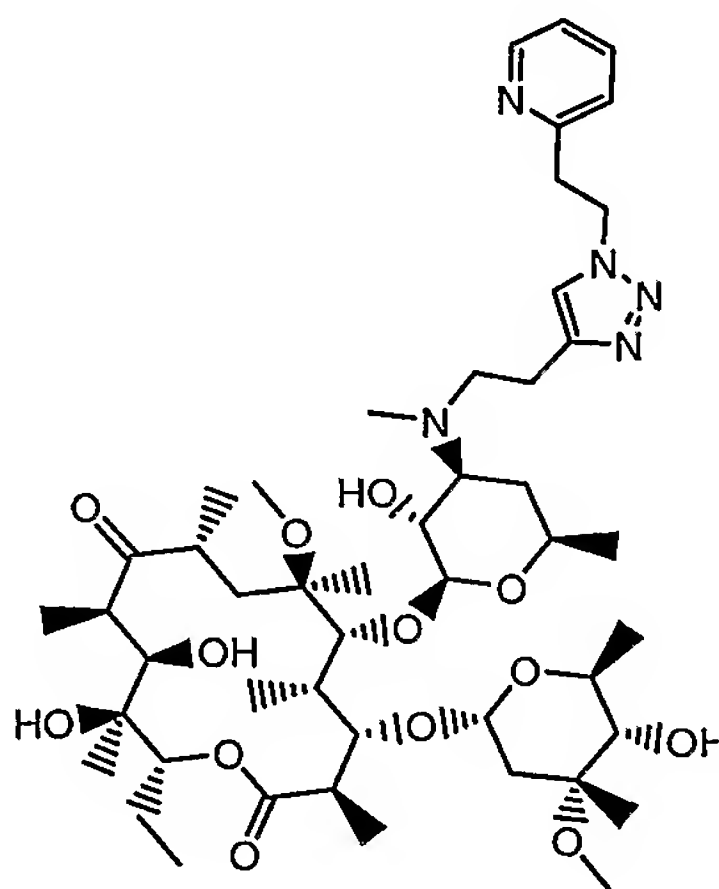
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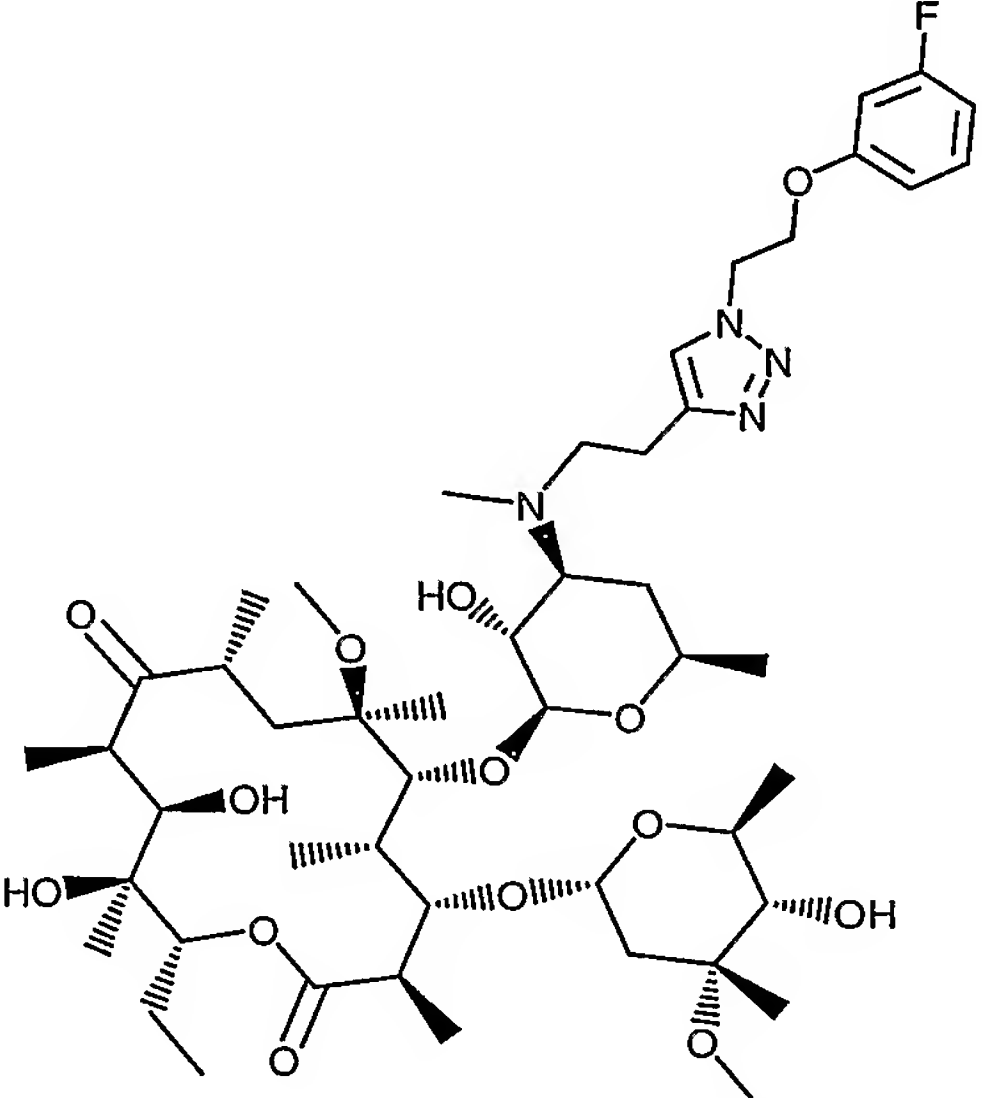
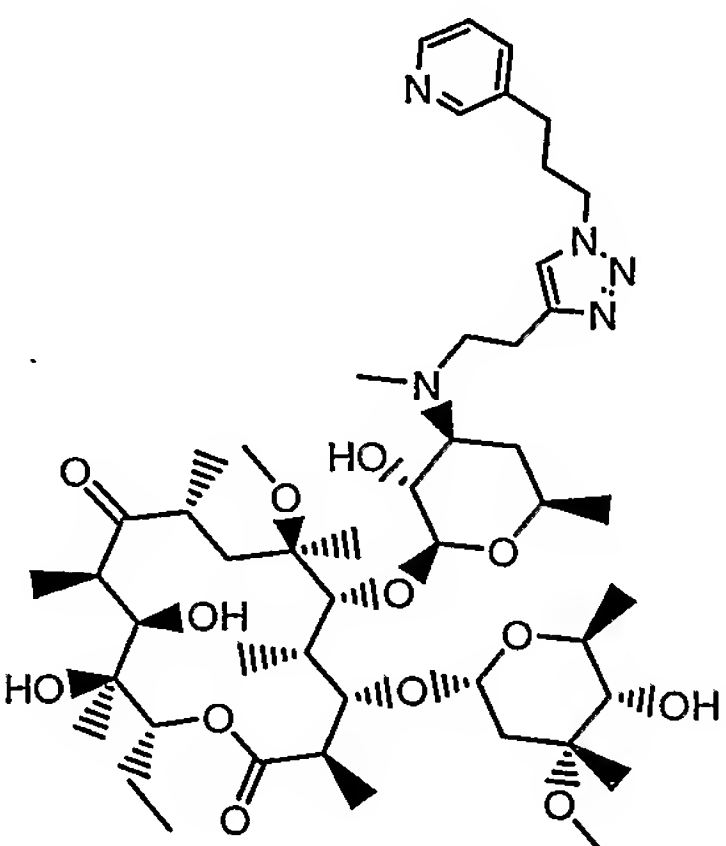
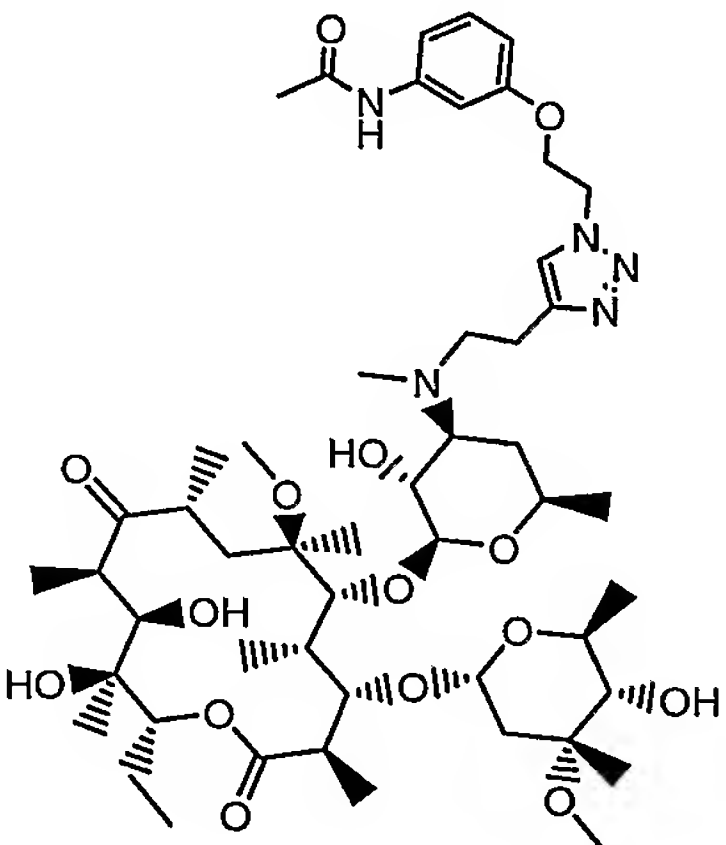
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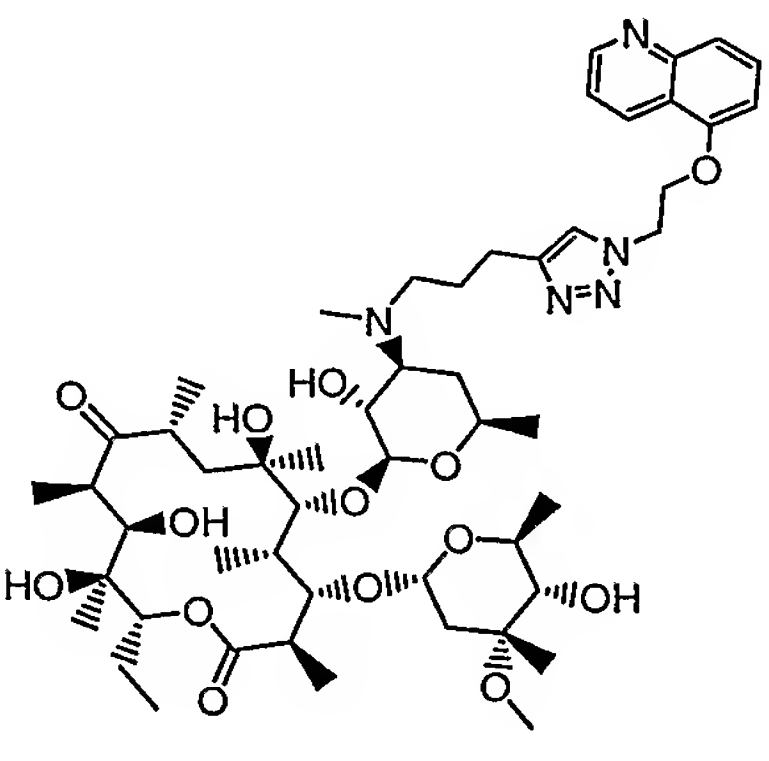
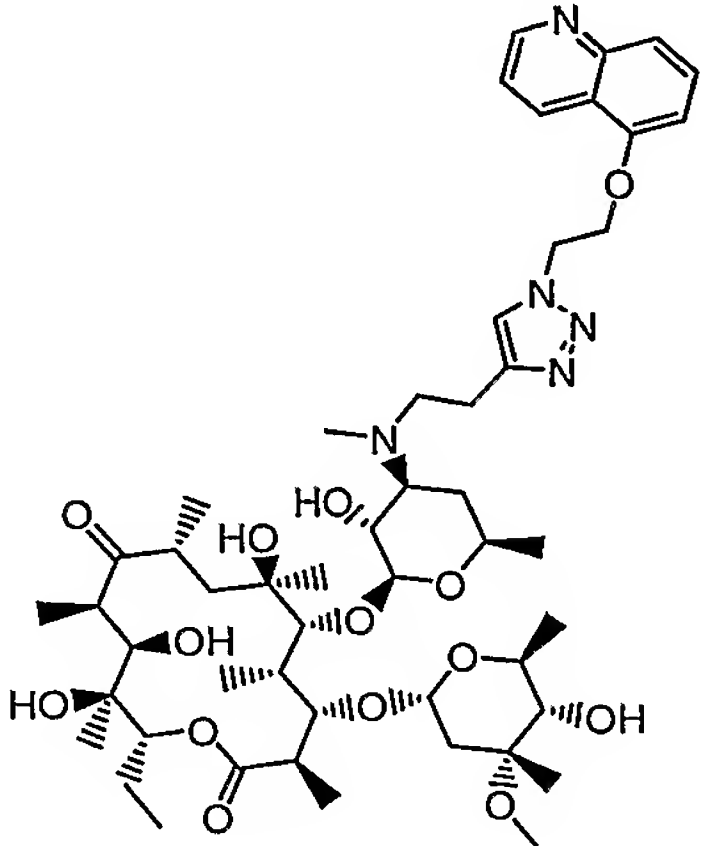
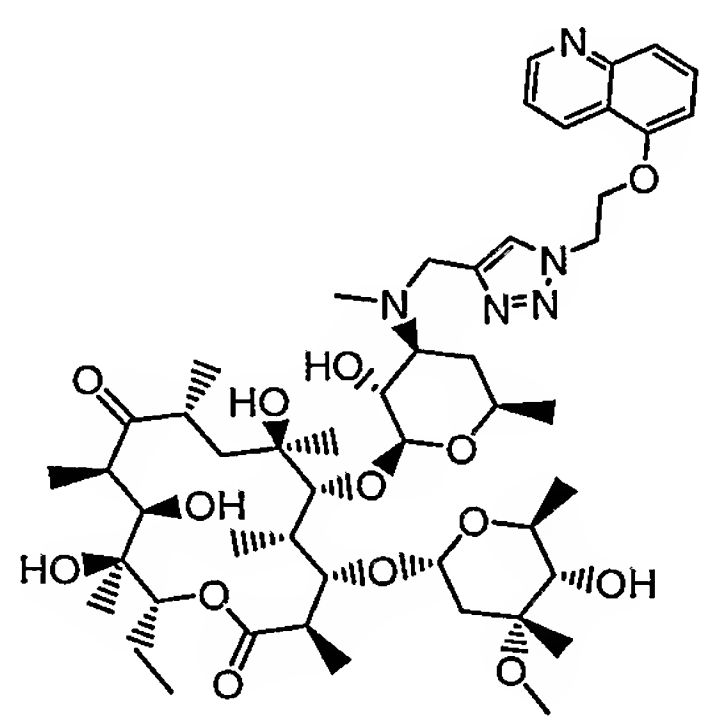
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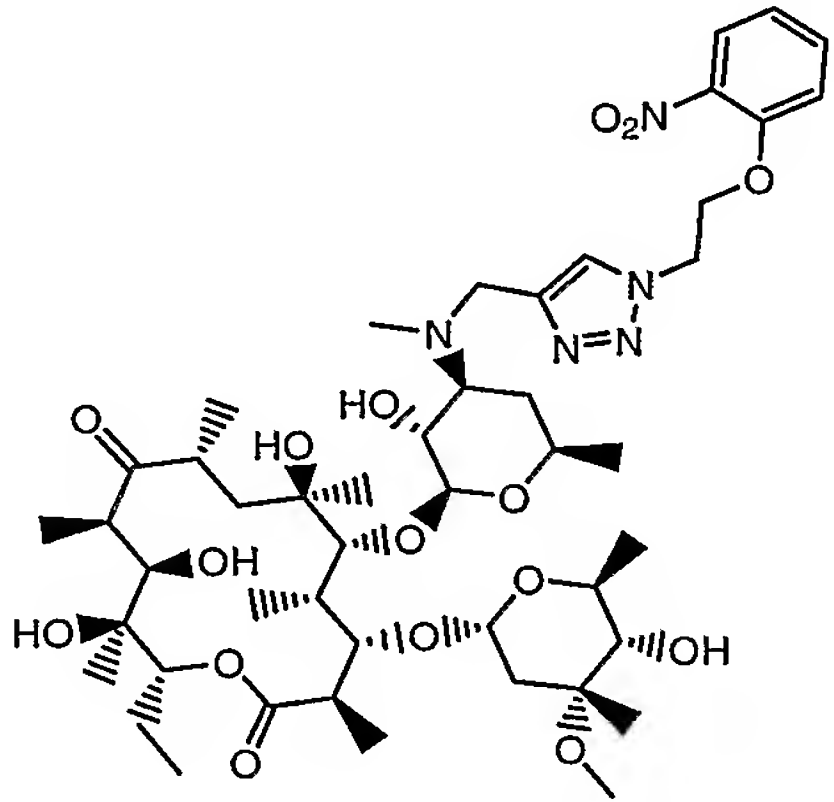
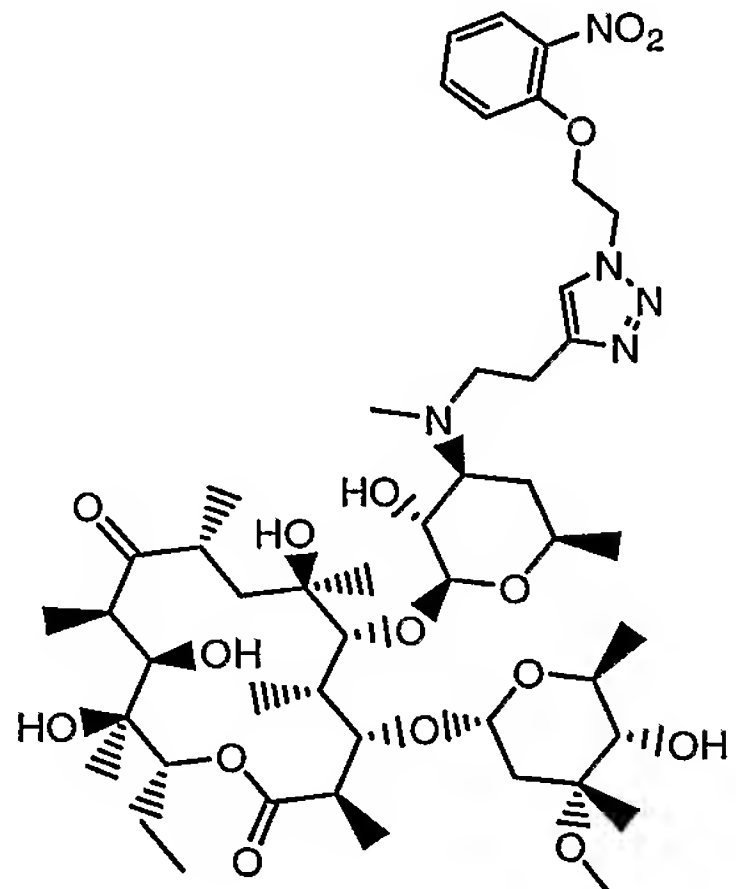
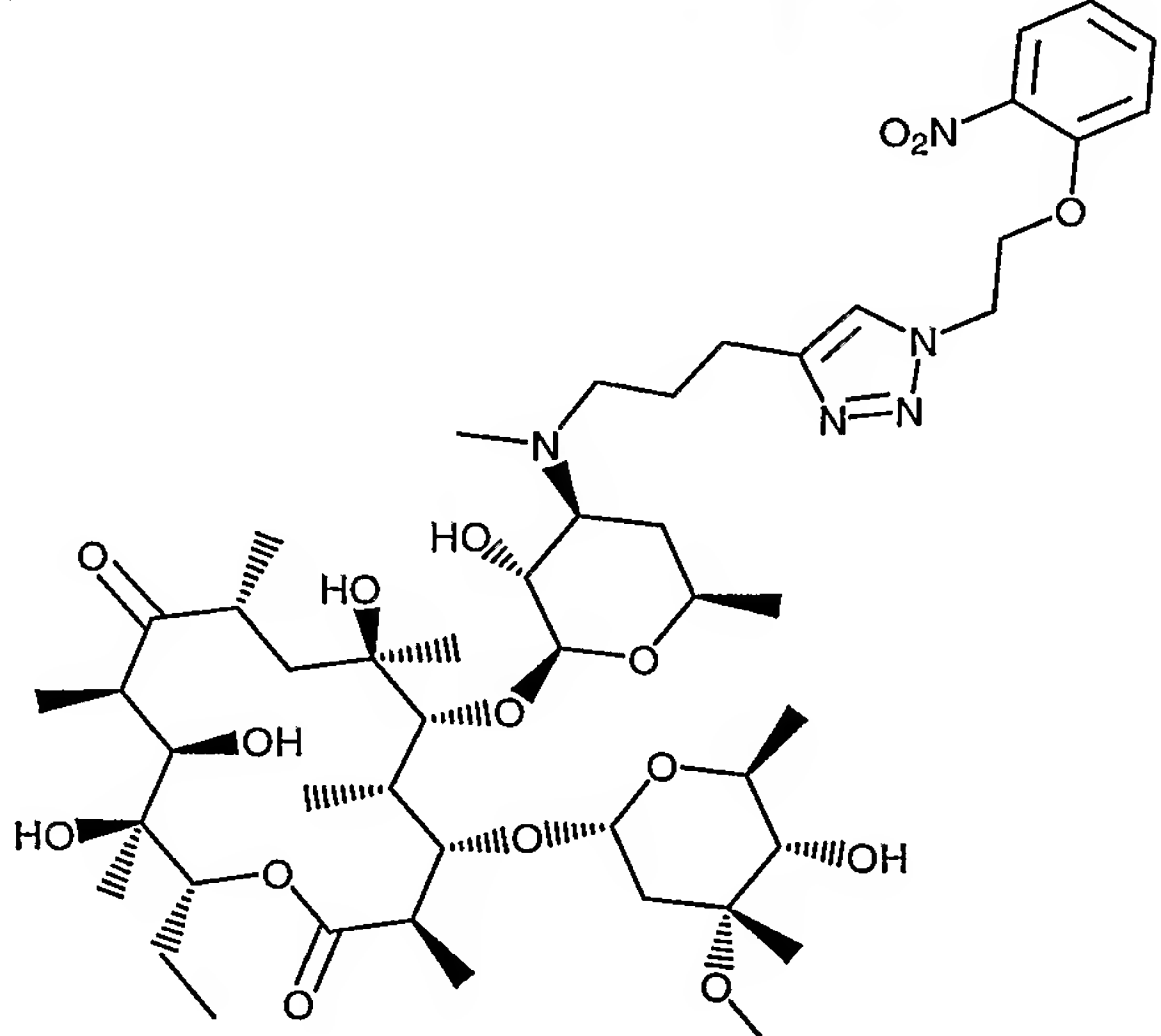
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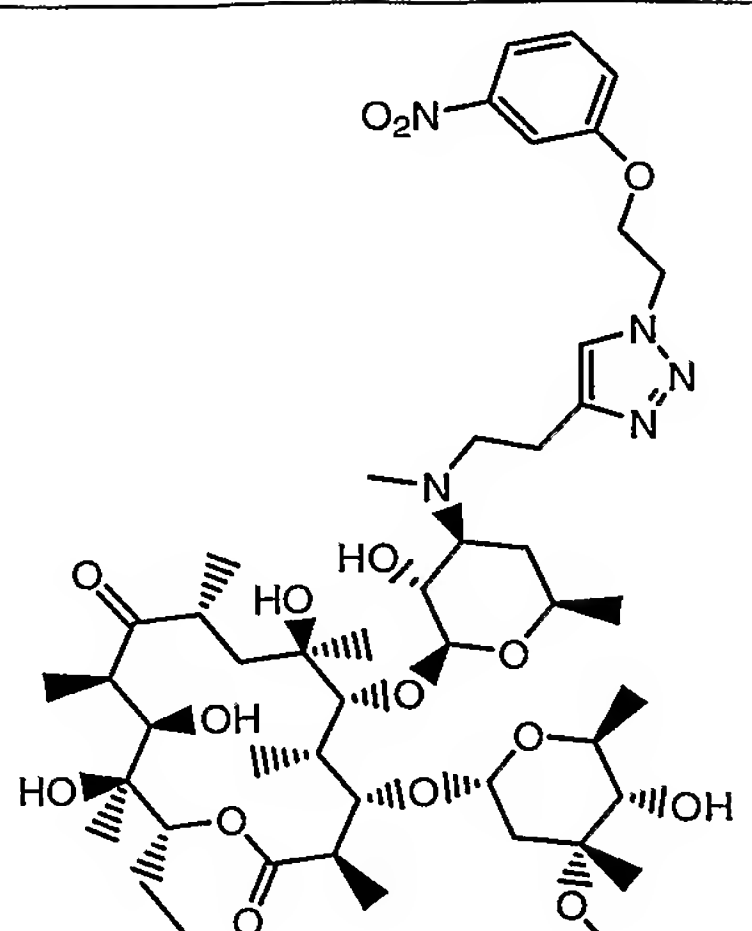
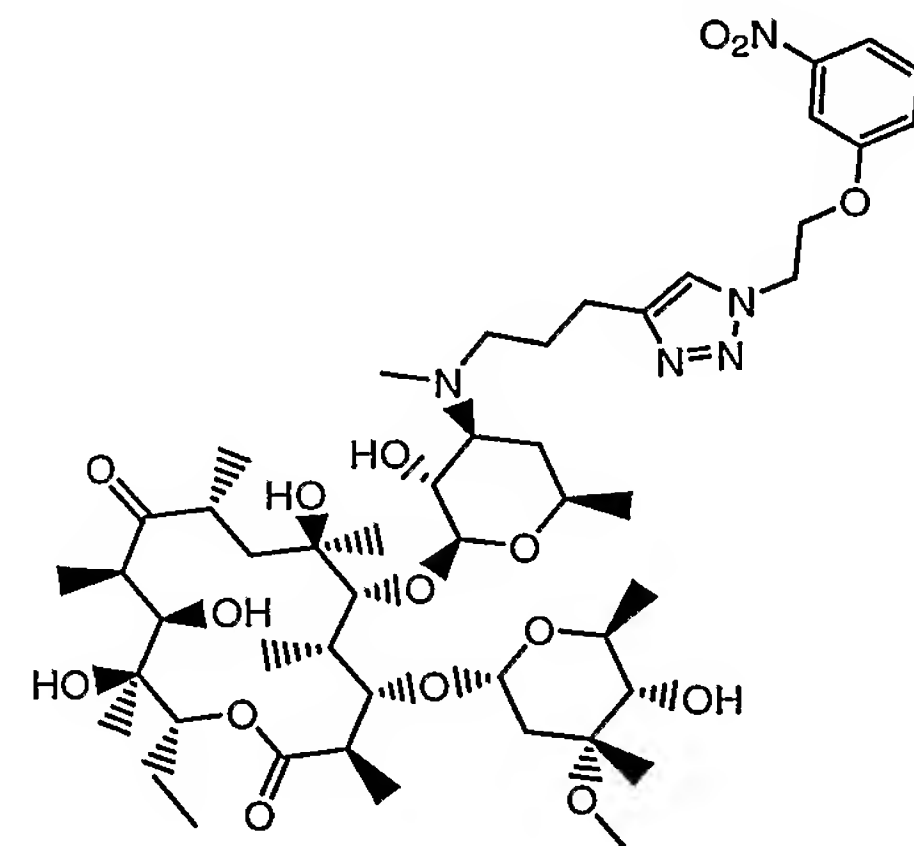
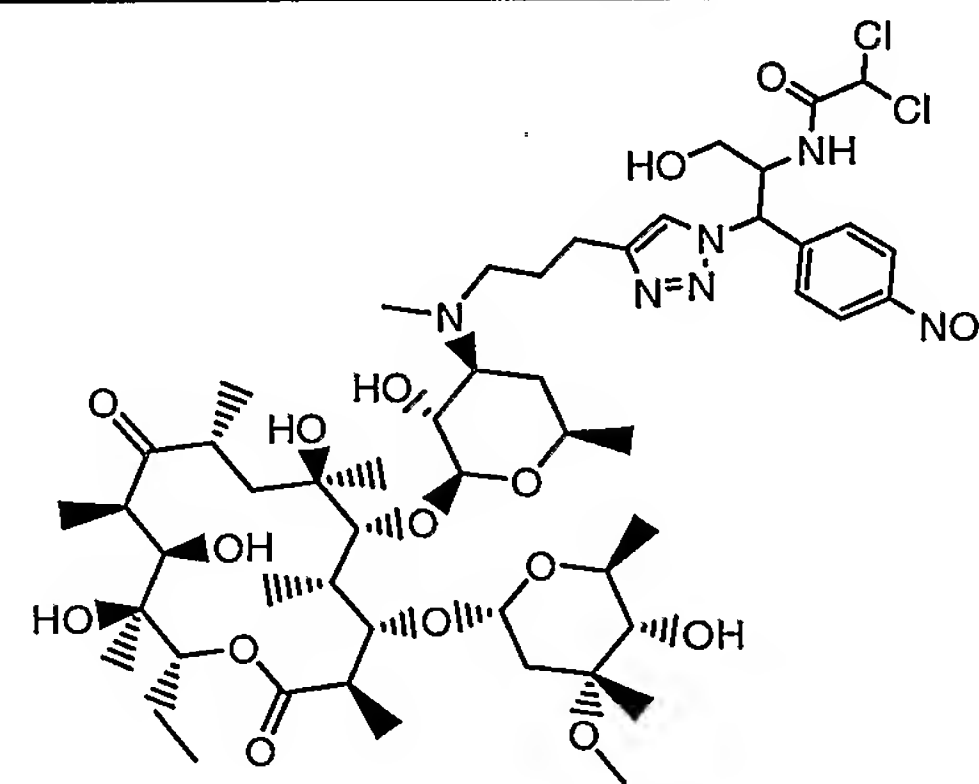
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337	 <p>Chemical structure 337 is a complex polycyclic molecule. It features a central core with multiple hydroxyl groups and a side chain containing a 1,2,3-triazole ring and a quinoline moiety. The structure is highly detailed, showing stereochemistry and various functional groups.</p>
338	 <p>Chemical structure 338 is a complex polycyclic molecule. It features a central core with multiple hydroxyl groups and a side chain containing a 1,2,3-triazole ring and a quinoline moiety. The structure is highly detailed, showing stereochemistry and various functional groups.</p>
339	 <p>Chemical structure 339 is a complex polycyclic molecule. It features a central core with multiple hydroxyl groups and a side chain containing a 1,2,3-triazole ring and a quinoline moiety. The structure is highly detailed, showing stereochemistry and various functional groups.</p>

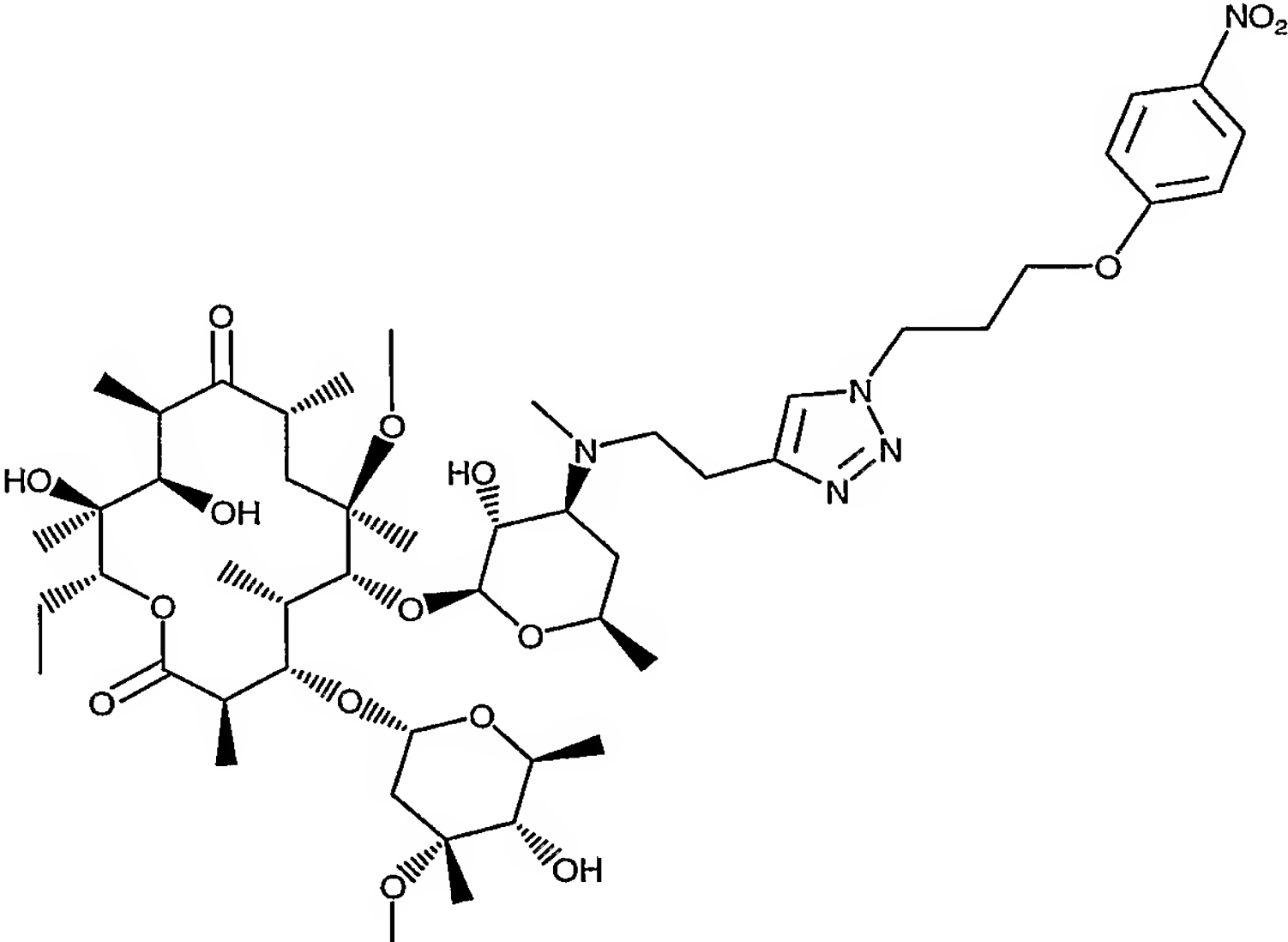
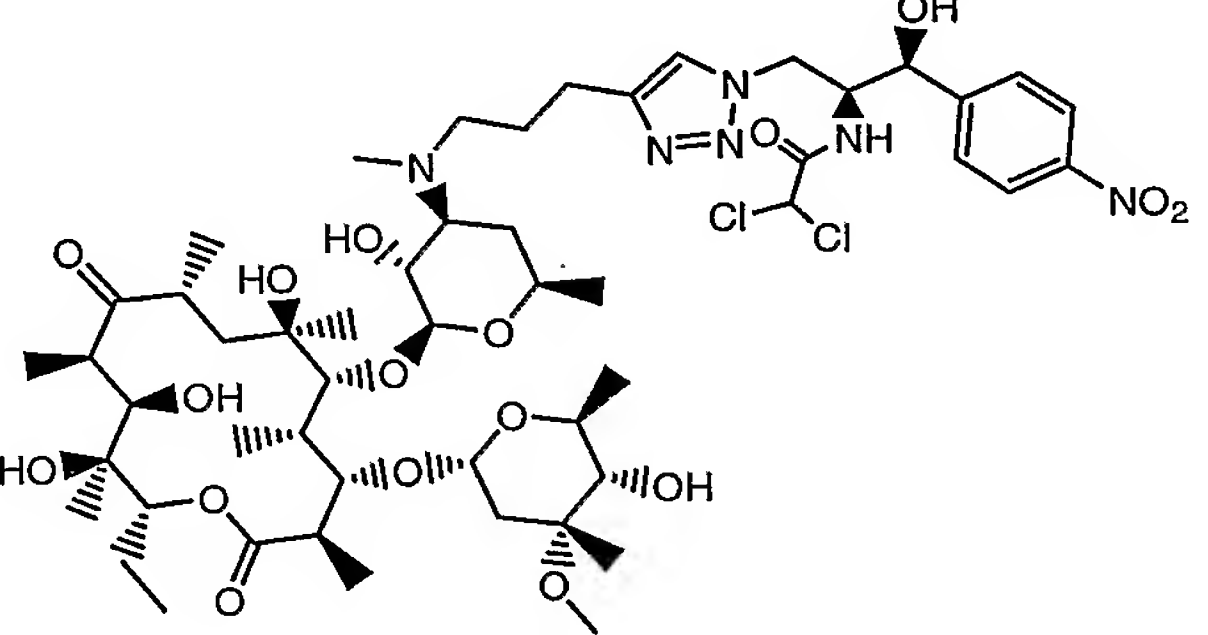
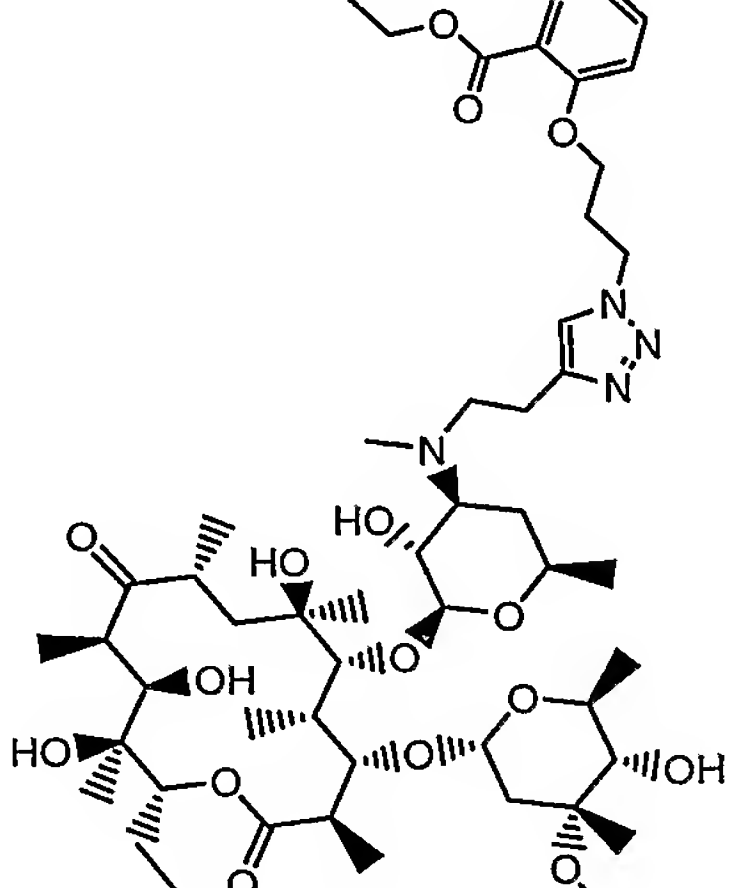
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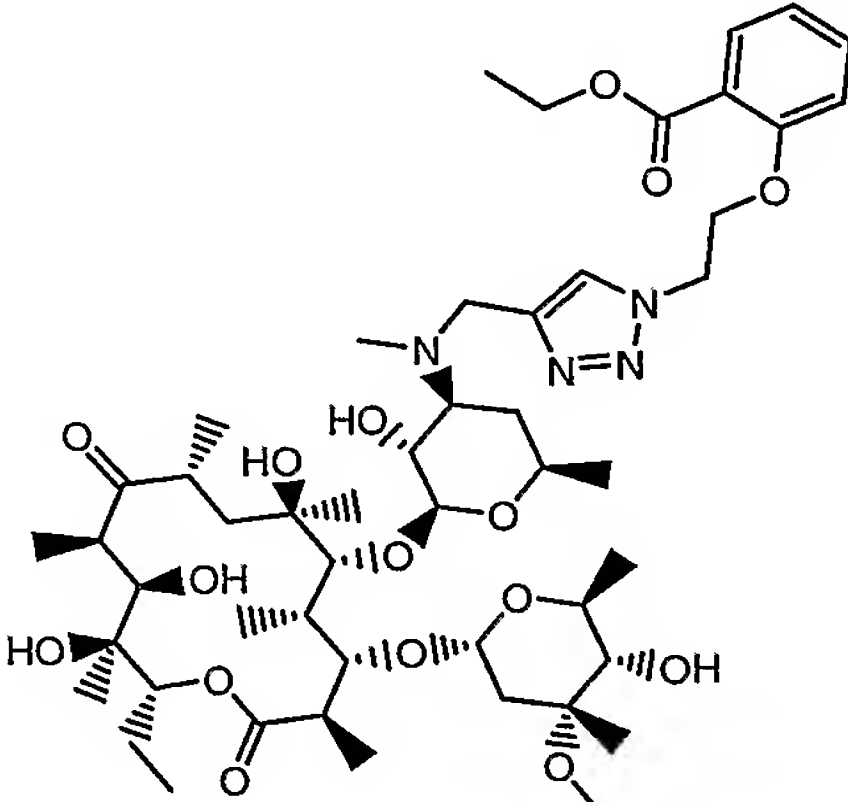
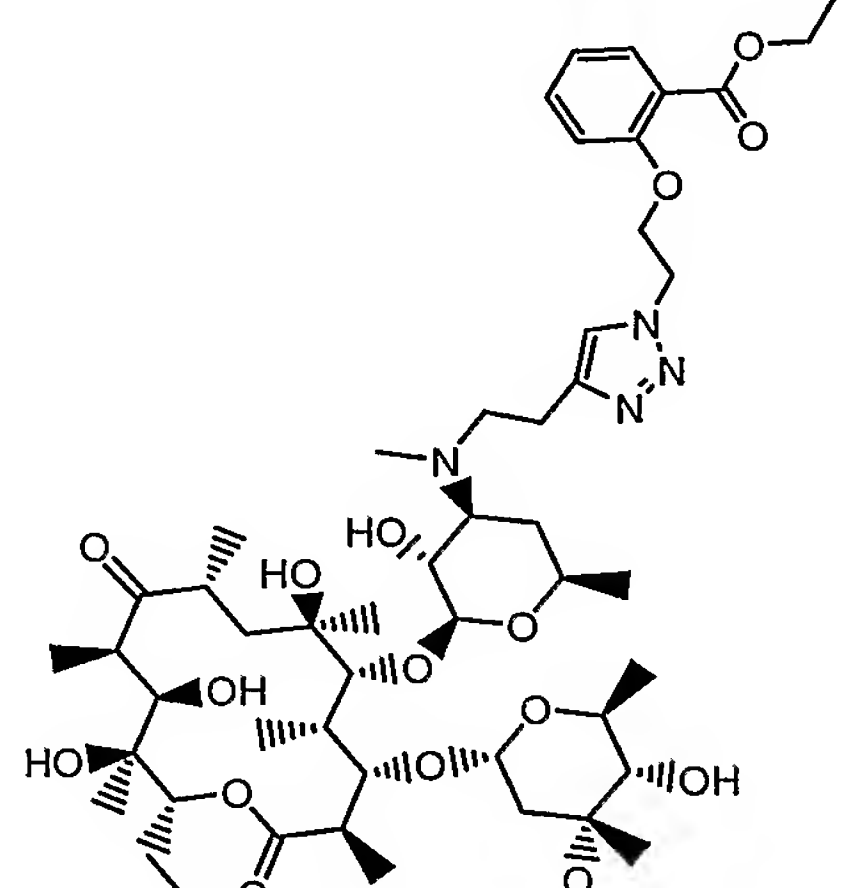
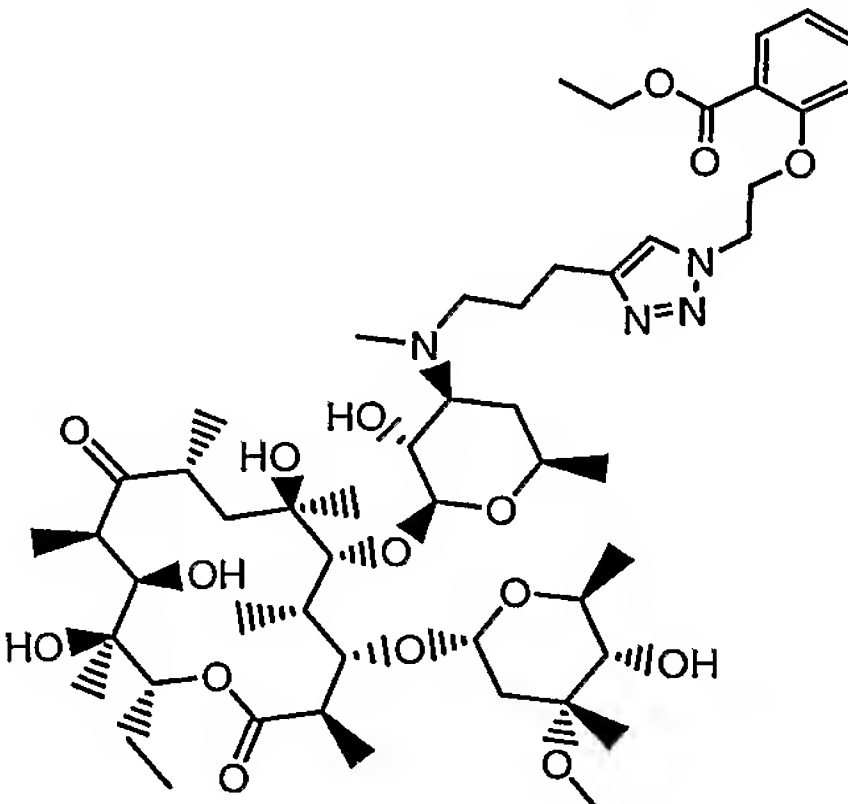
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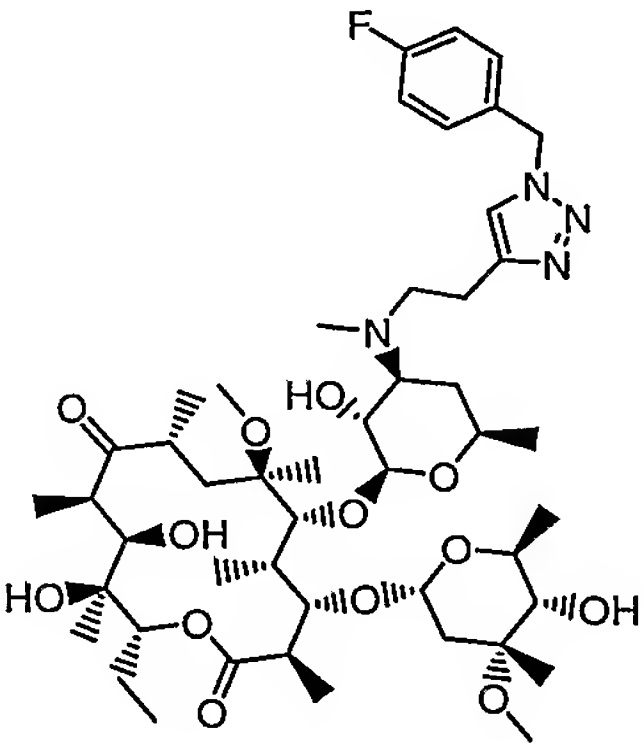
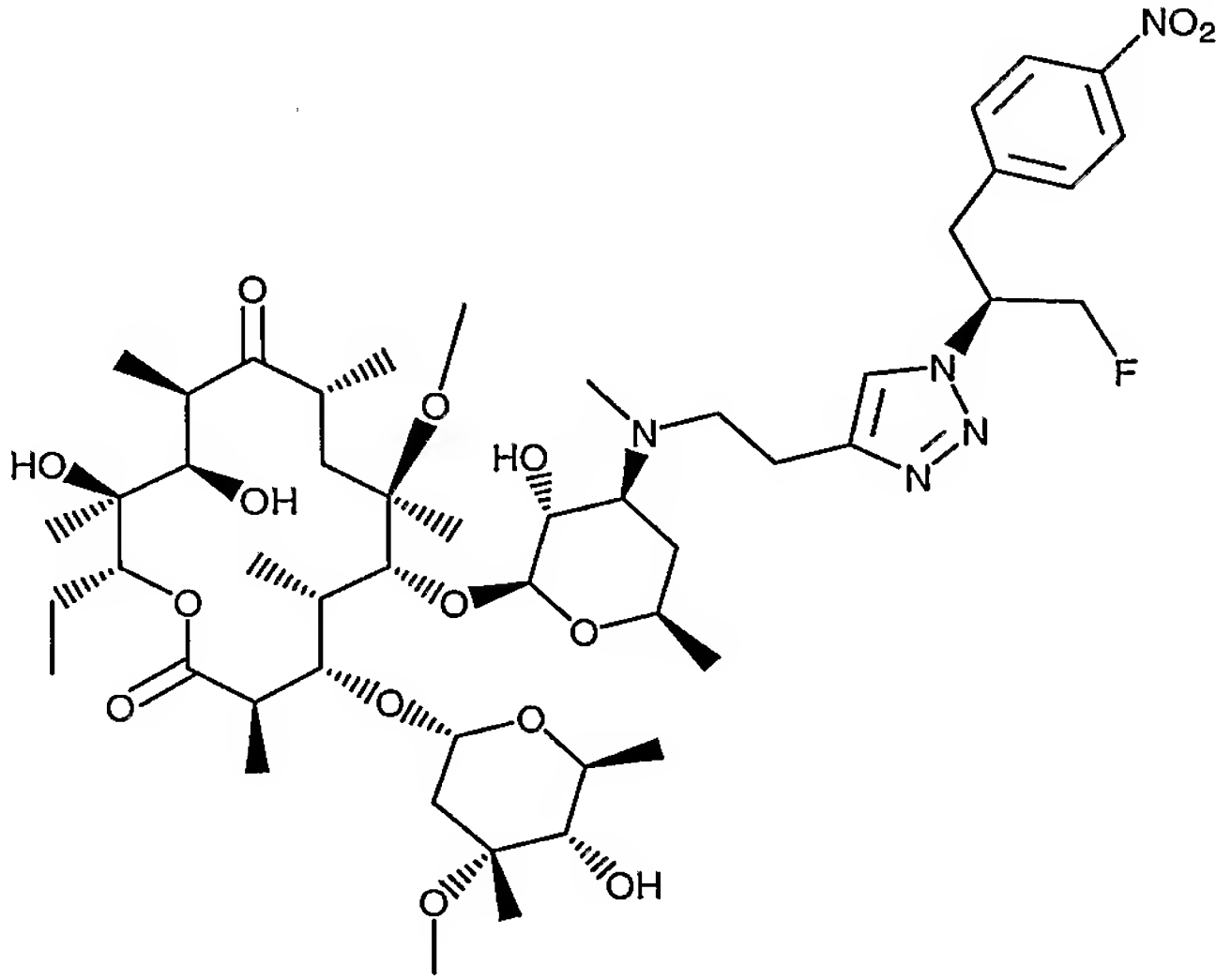
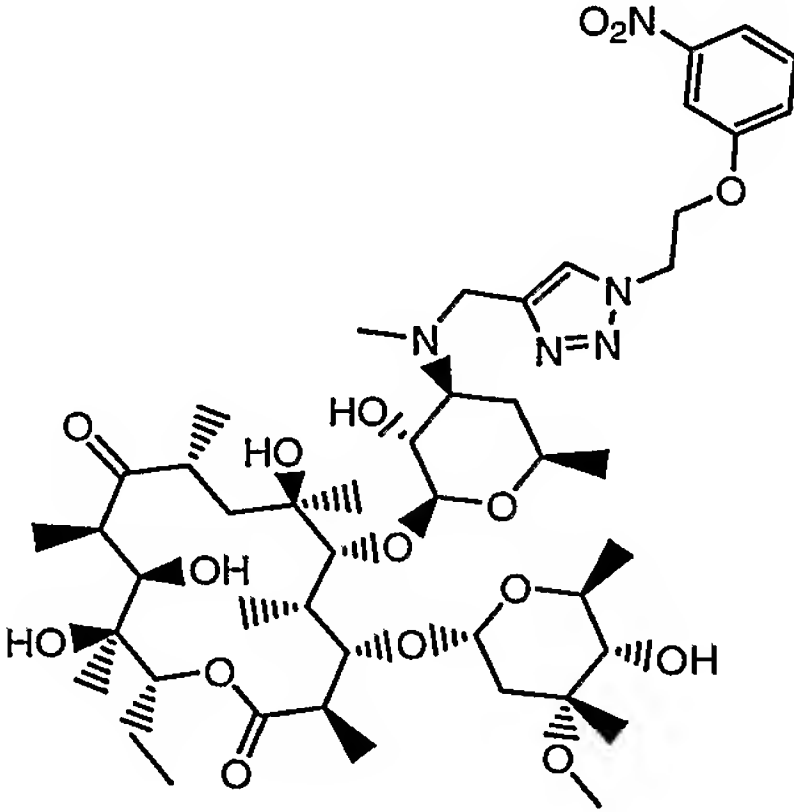
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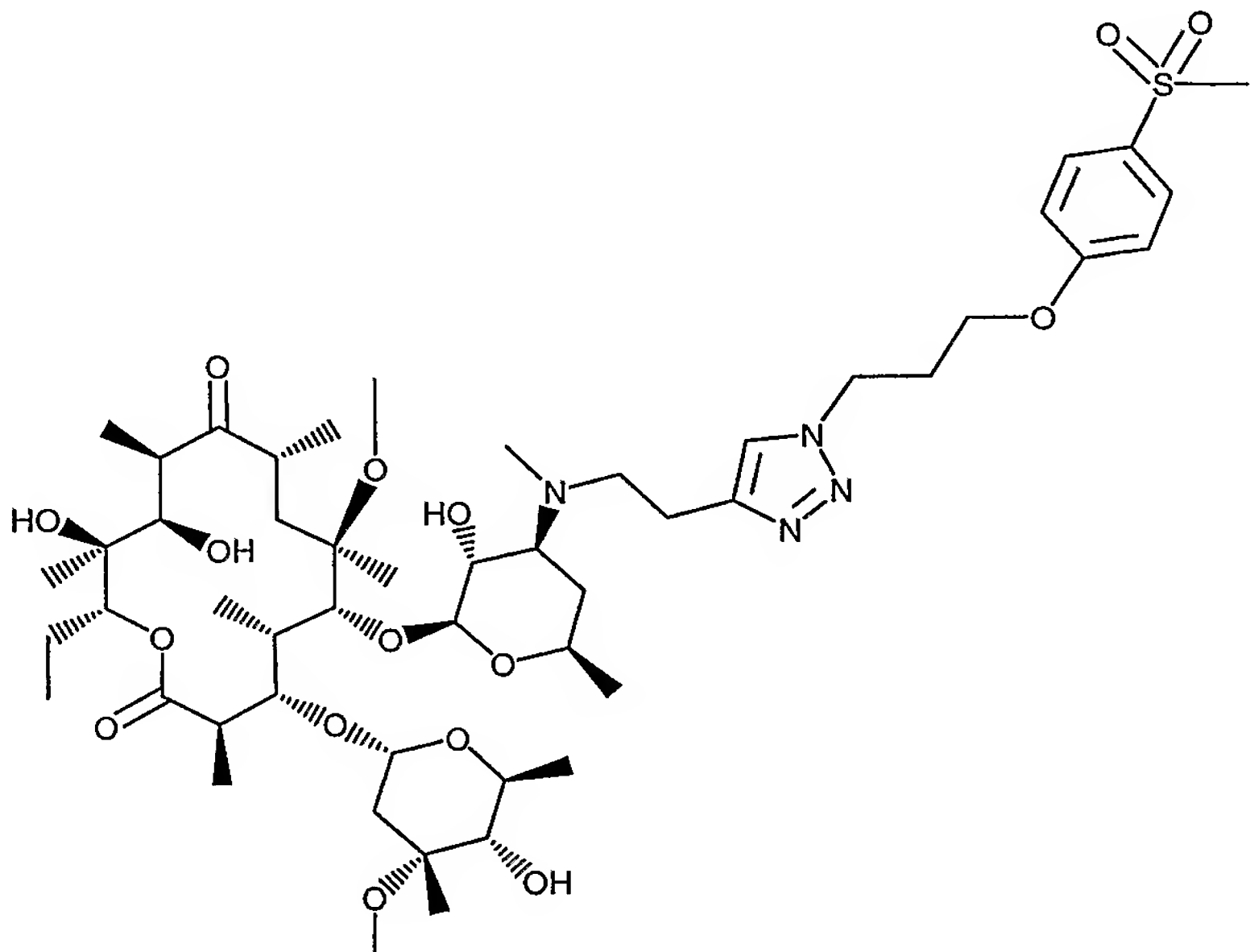
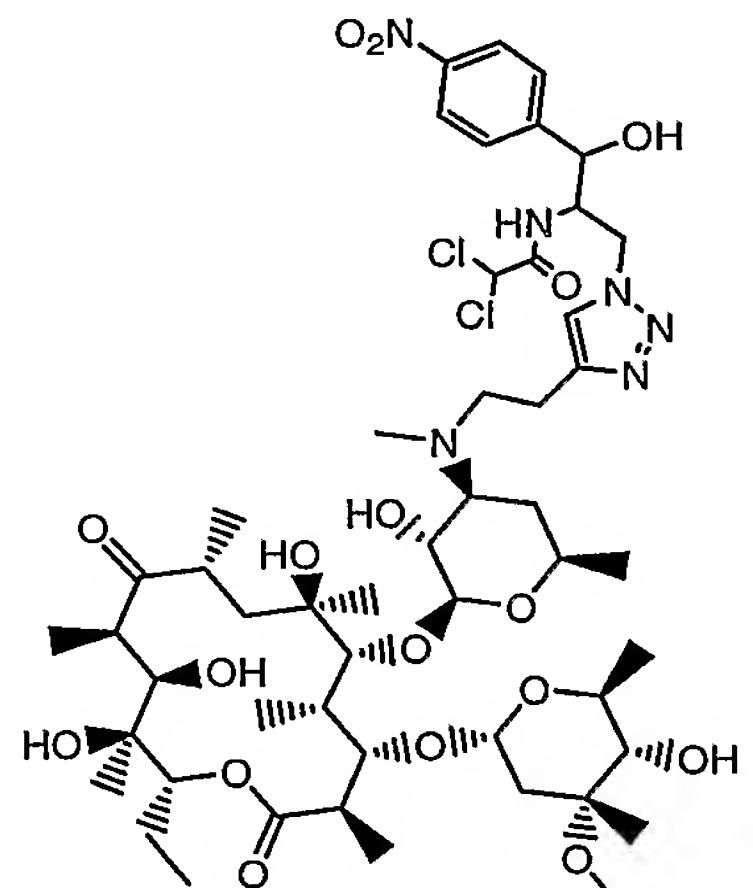
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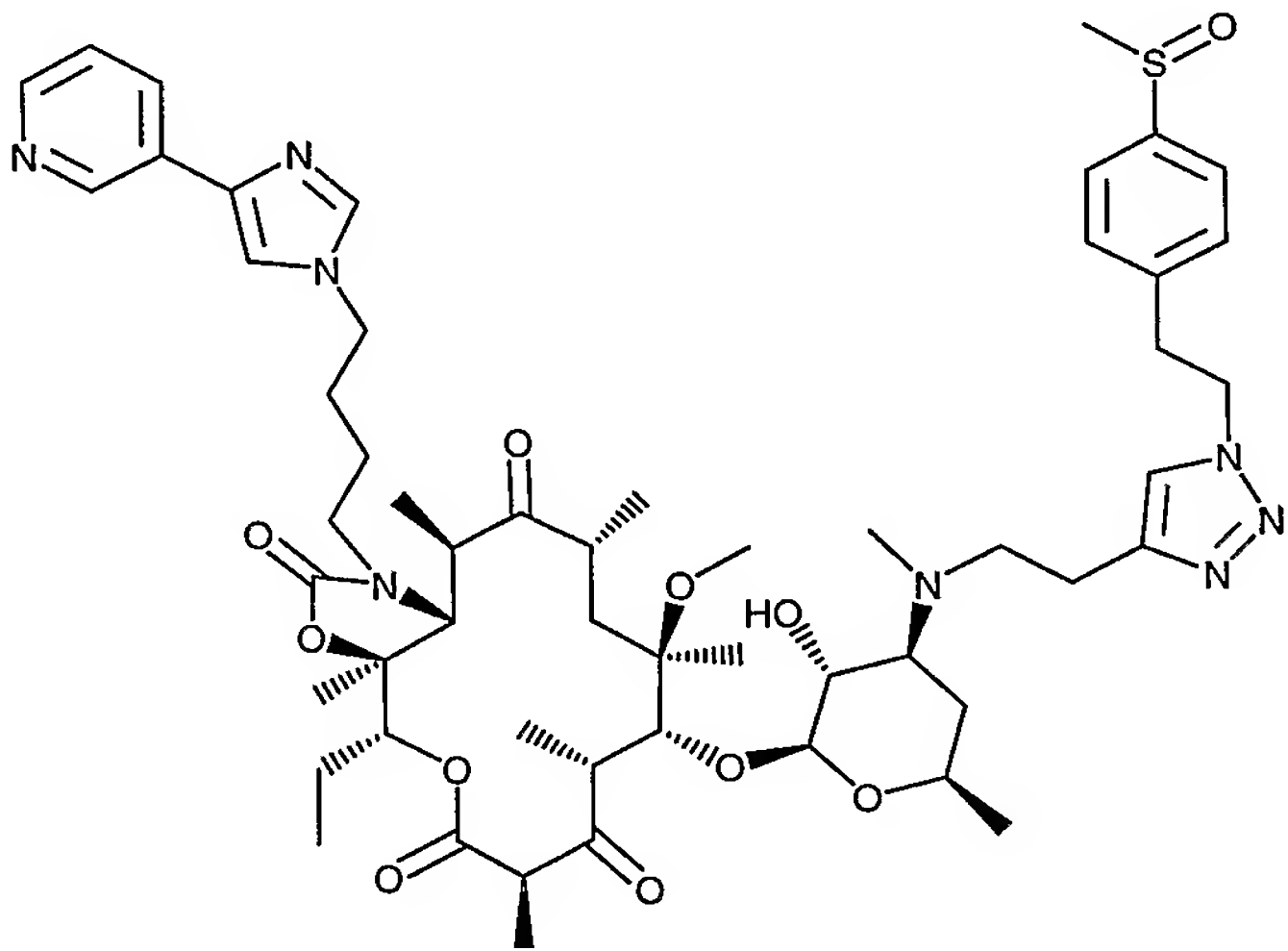
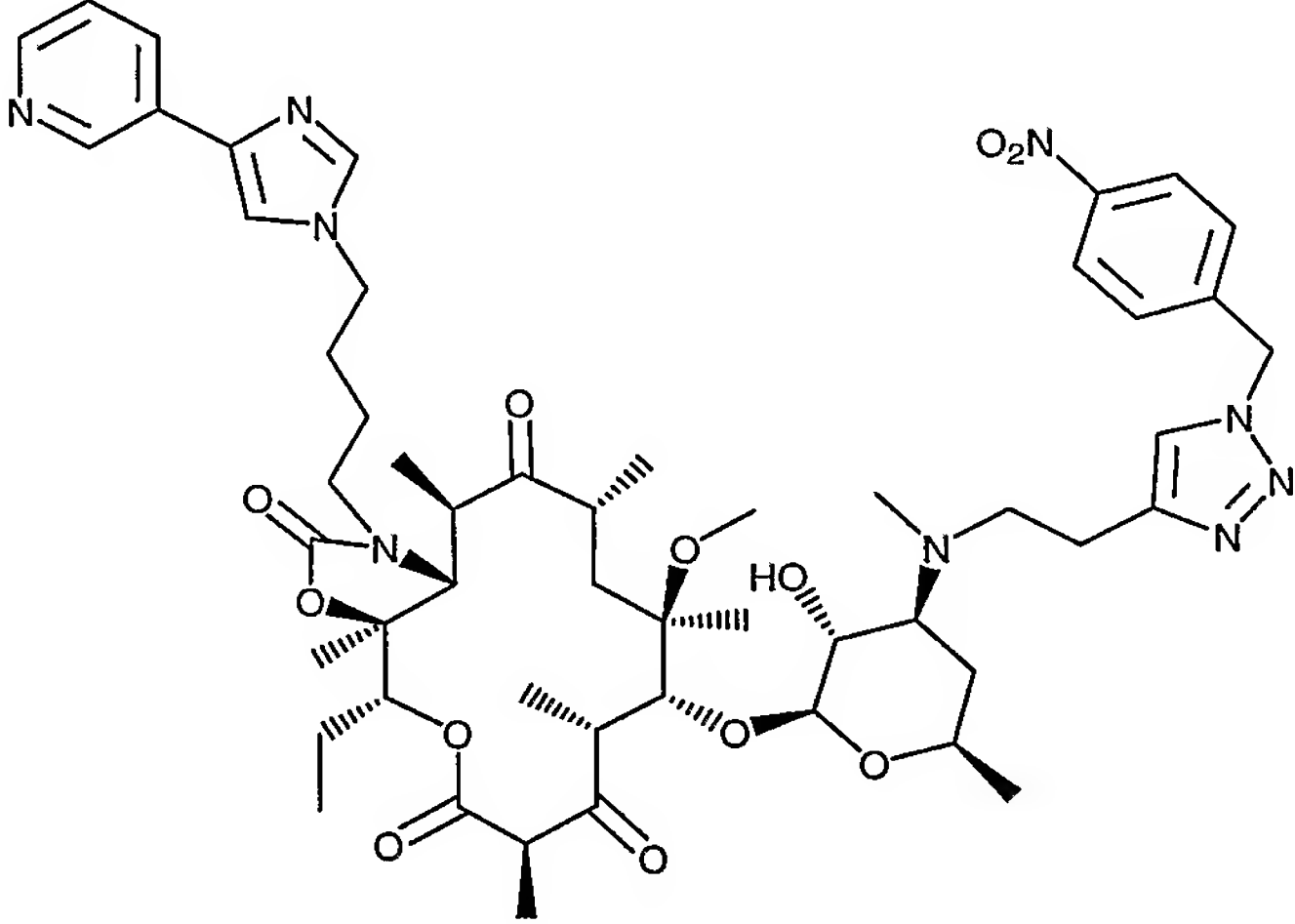
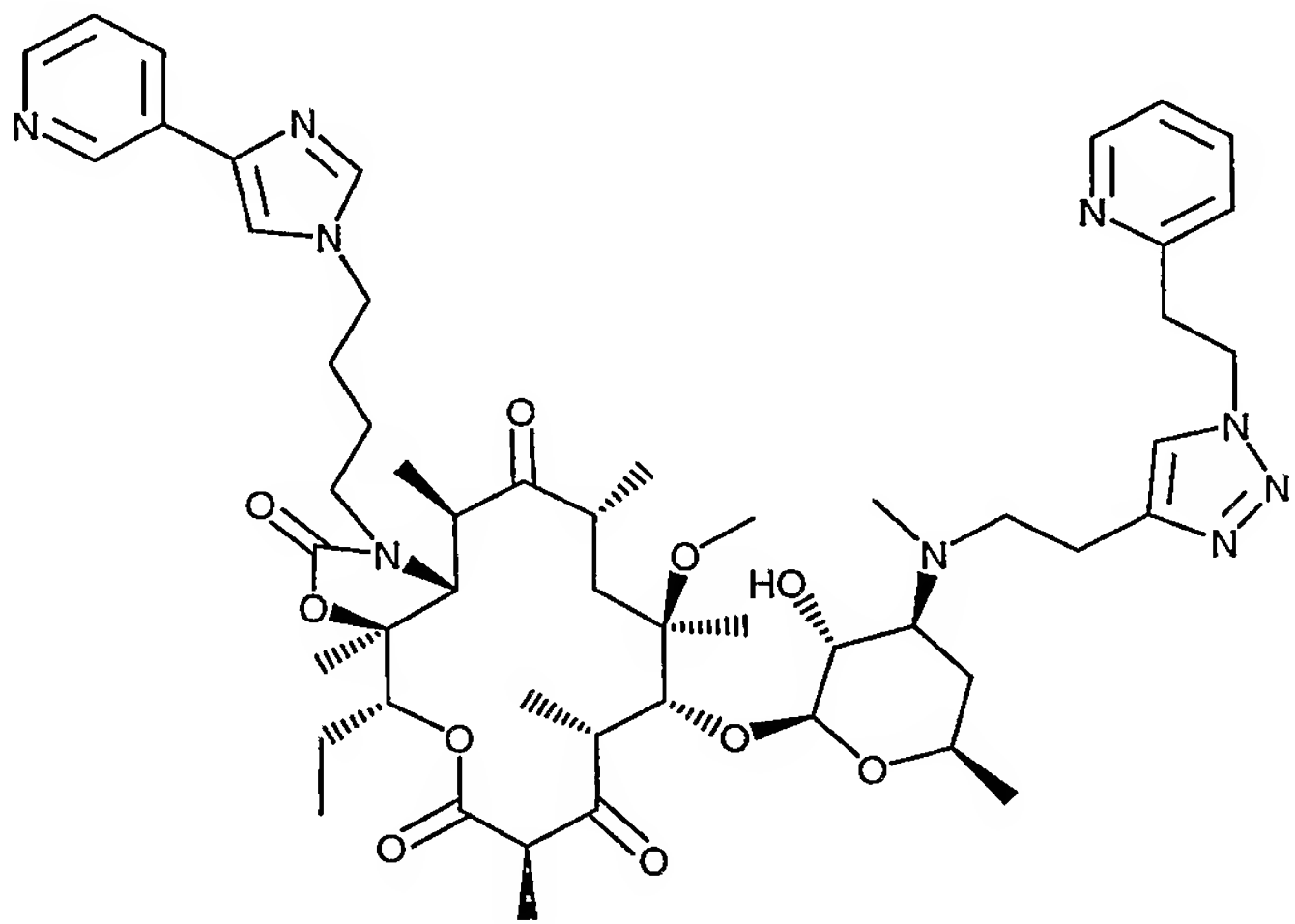
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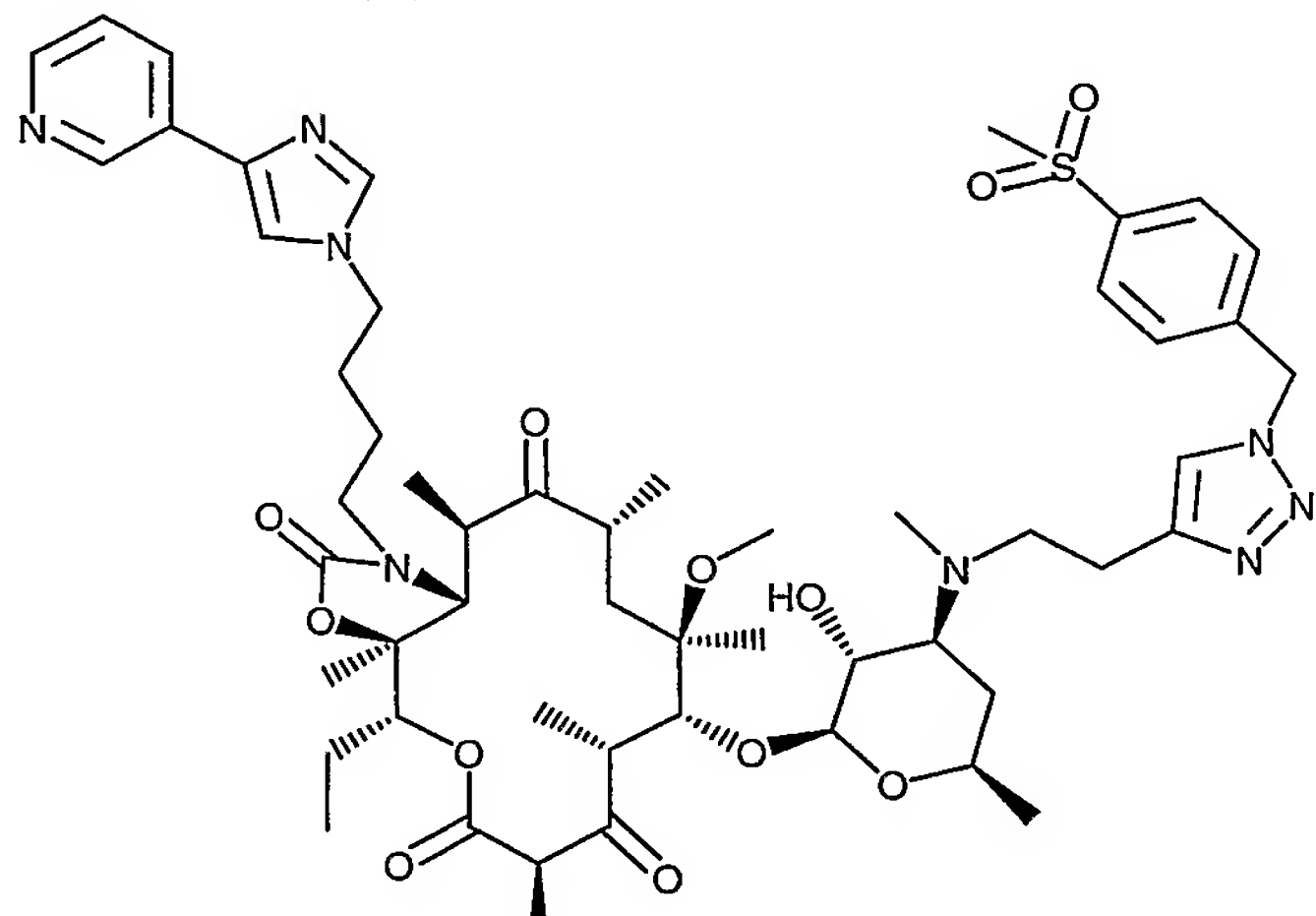
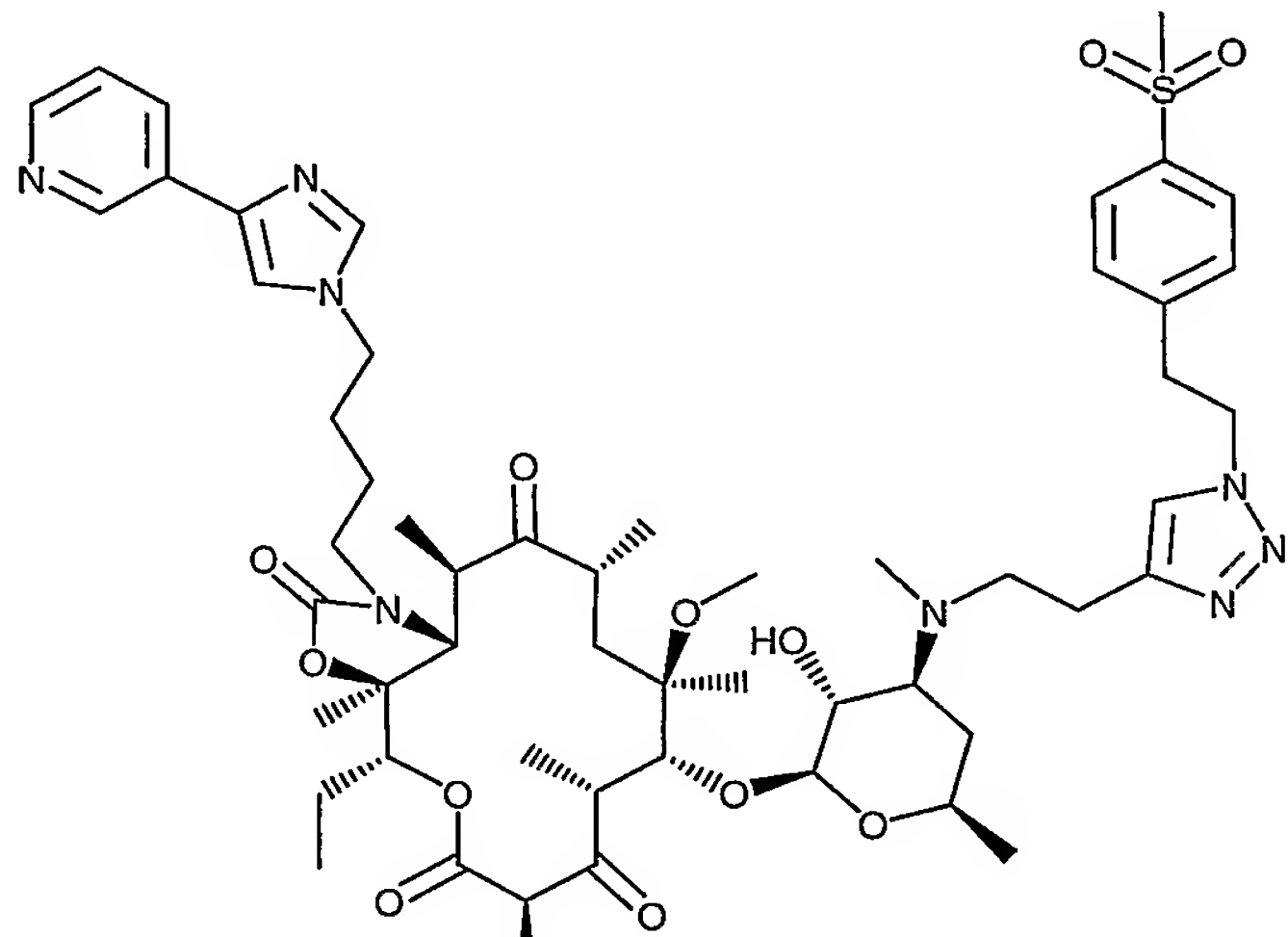
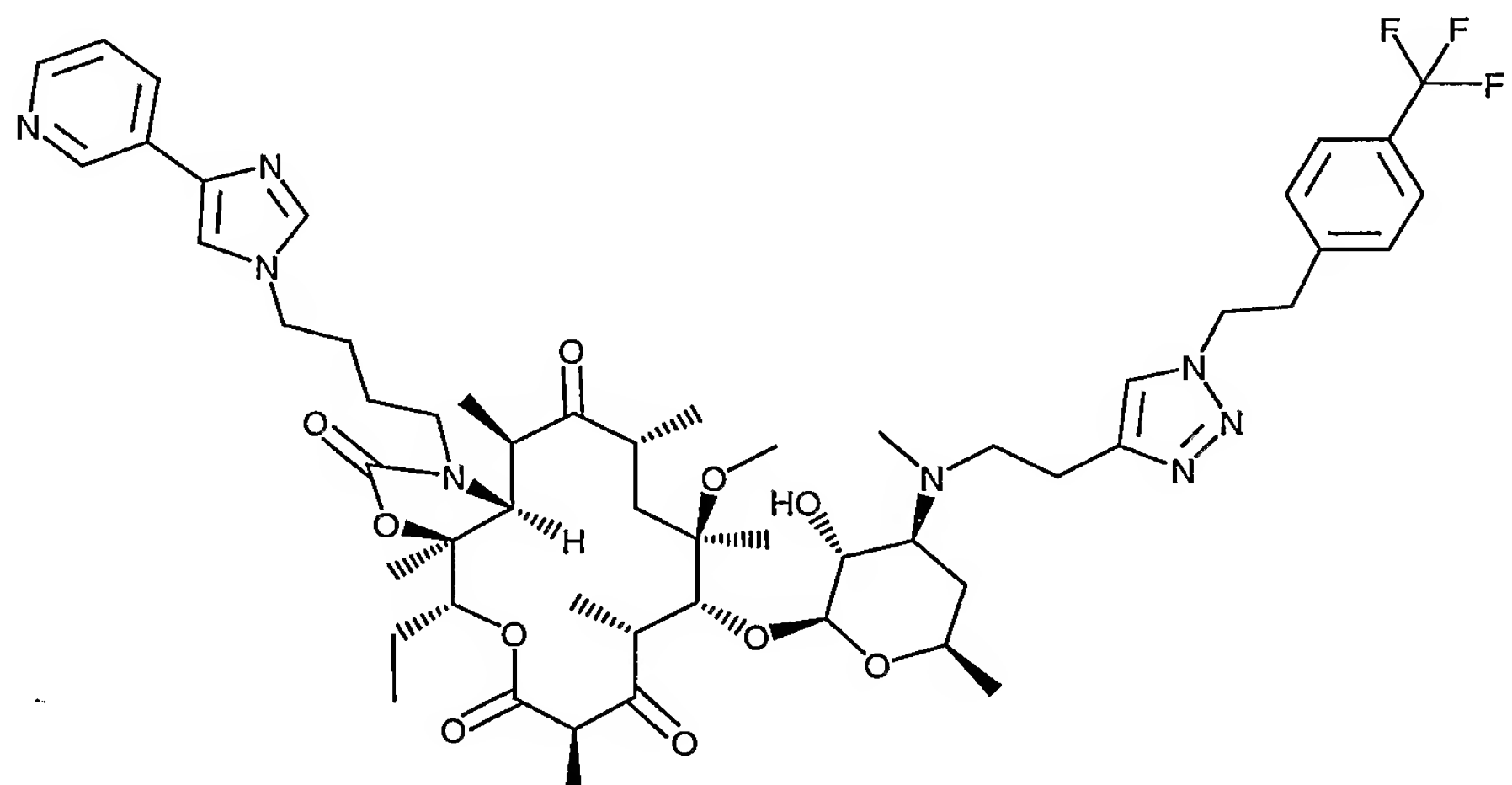
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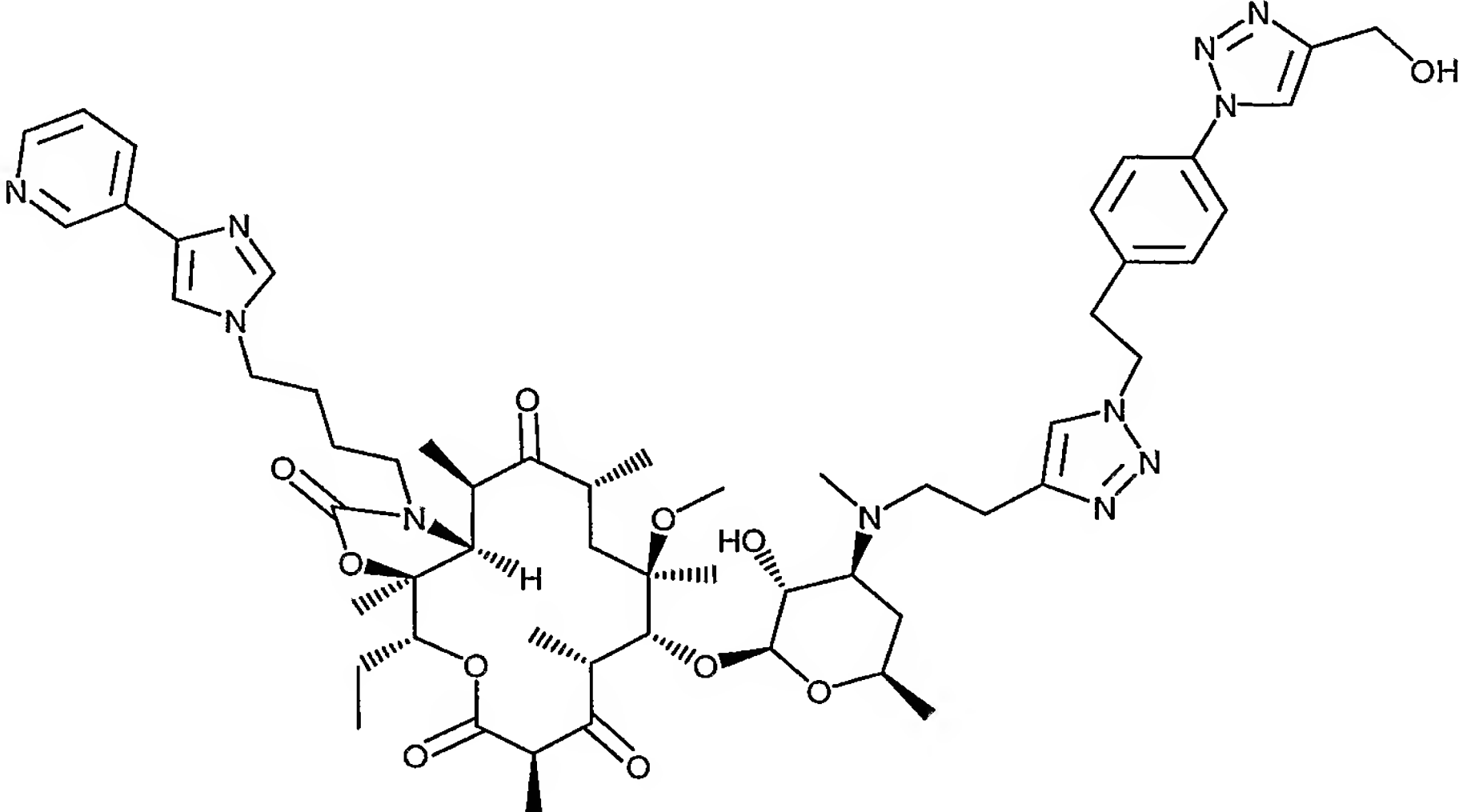
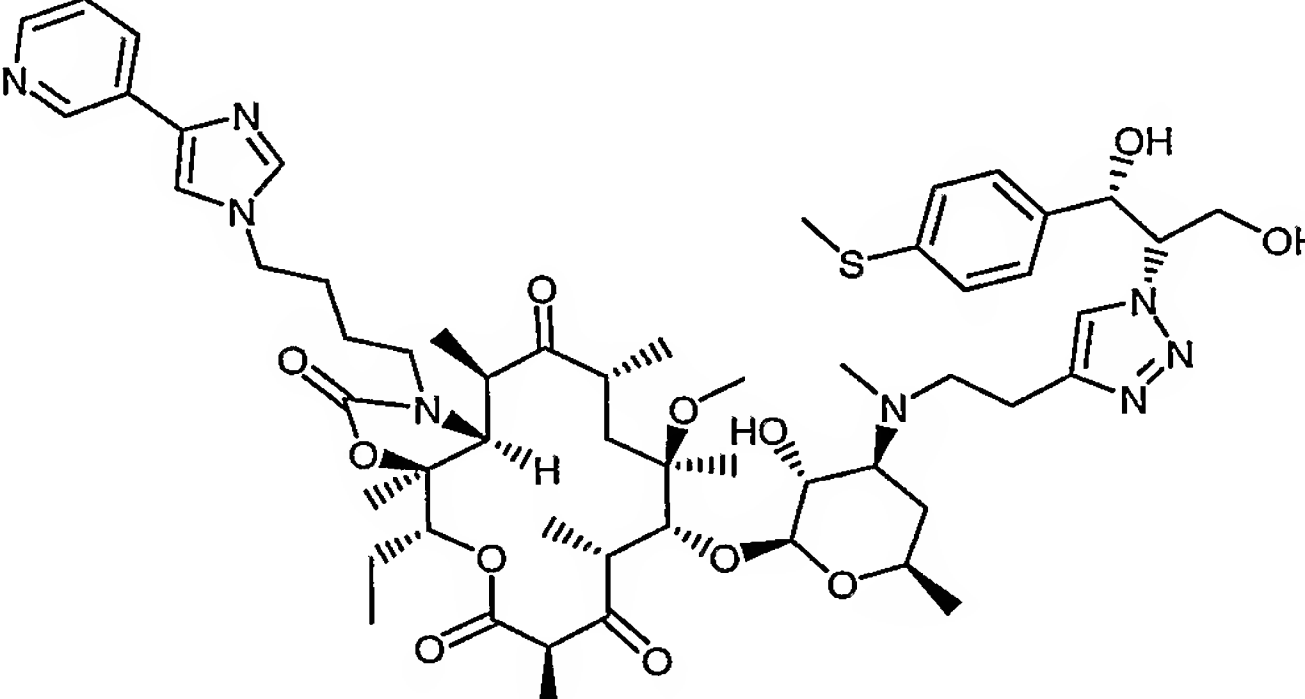
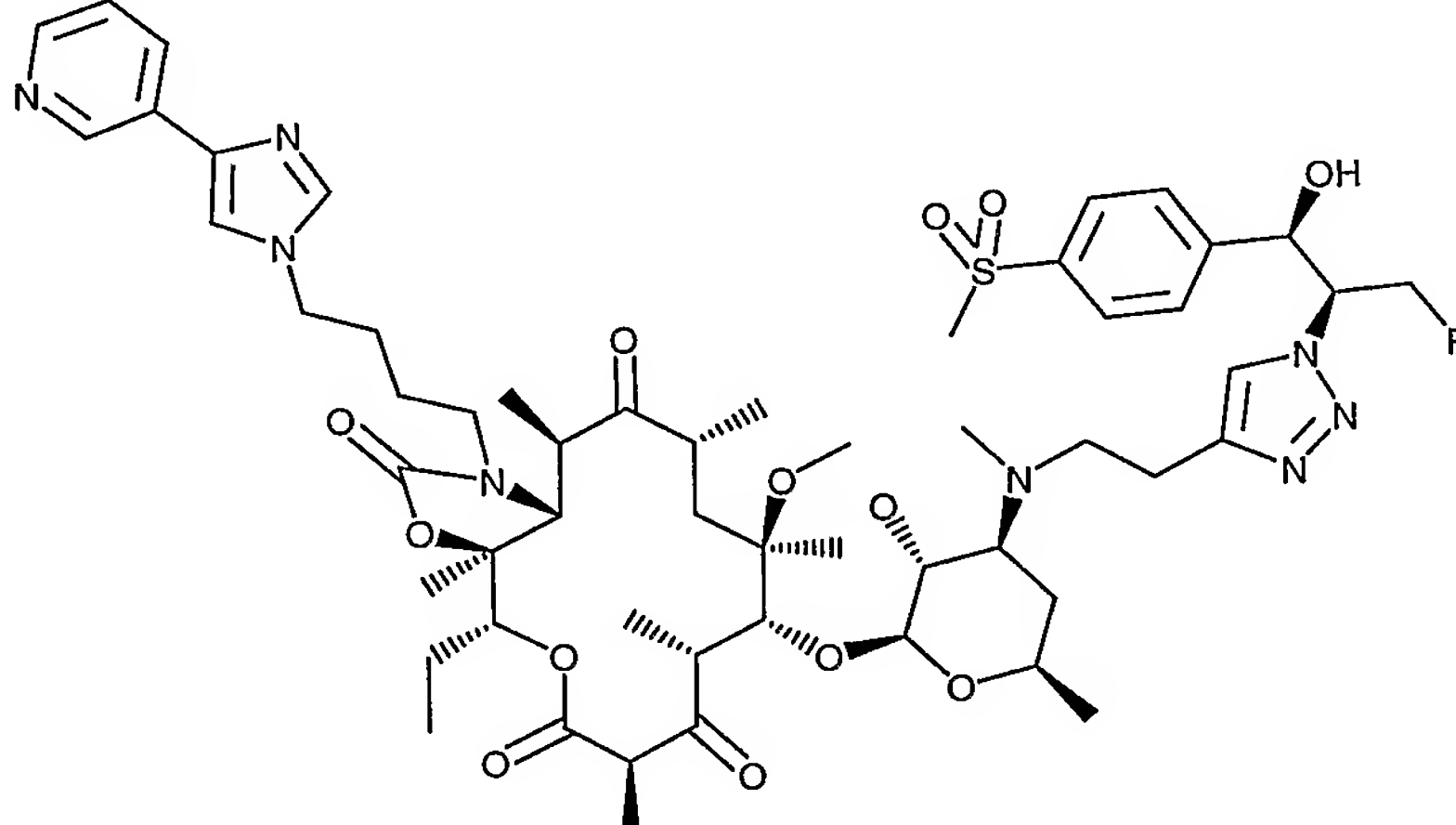
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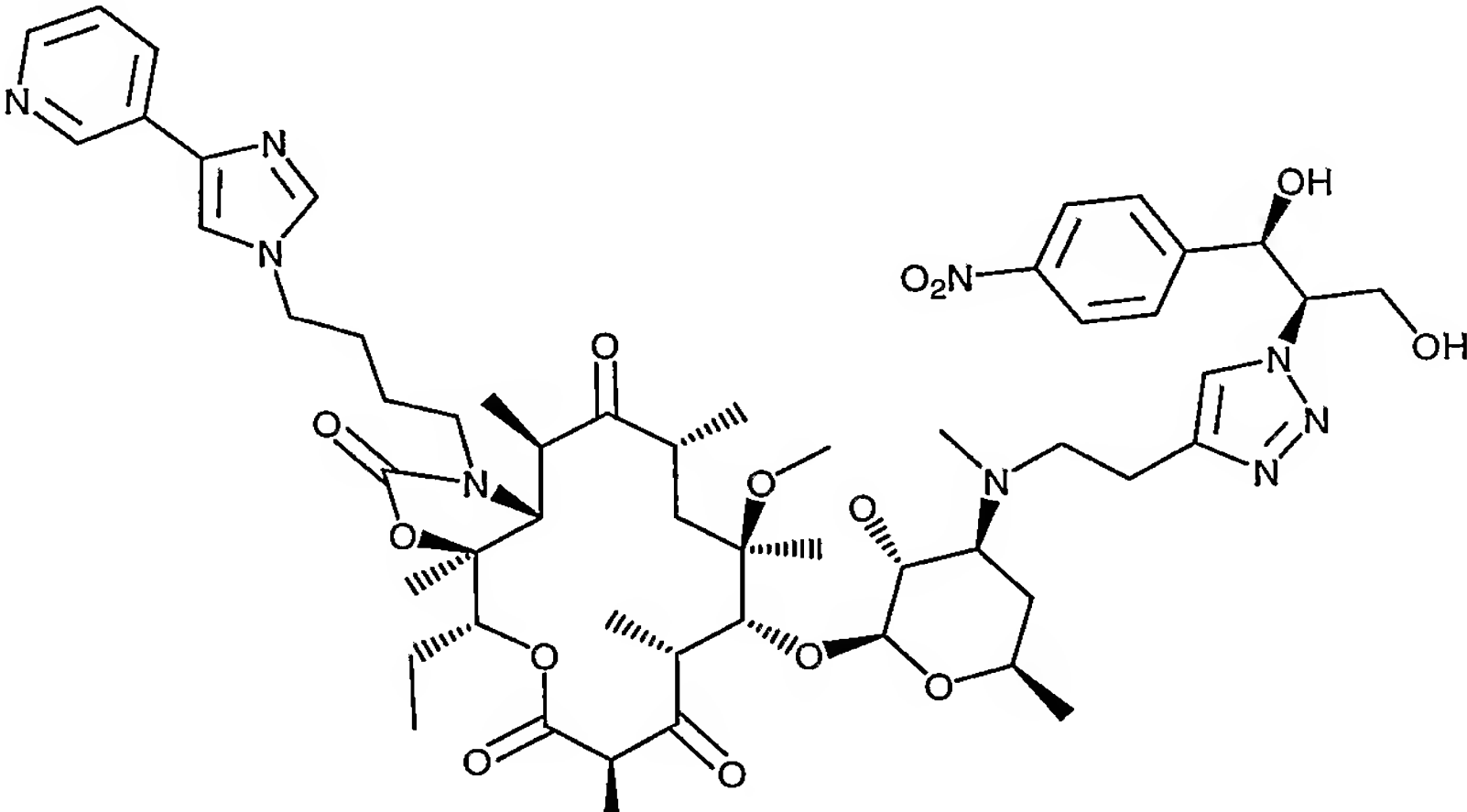
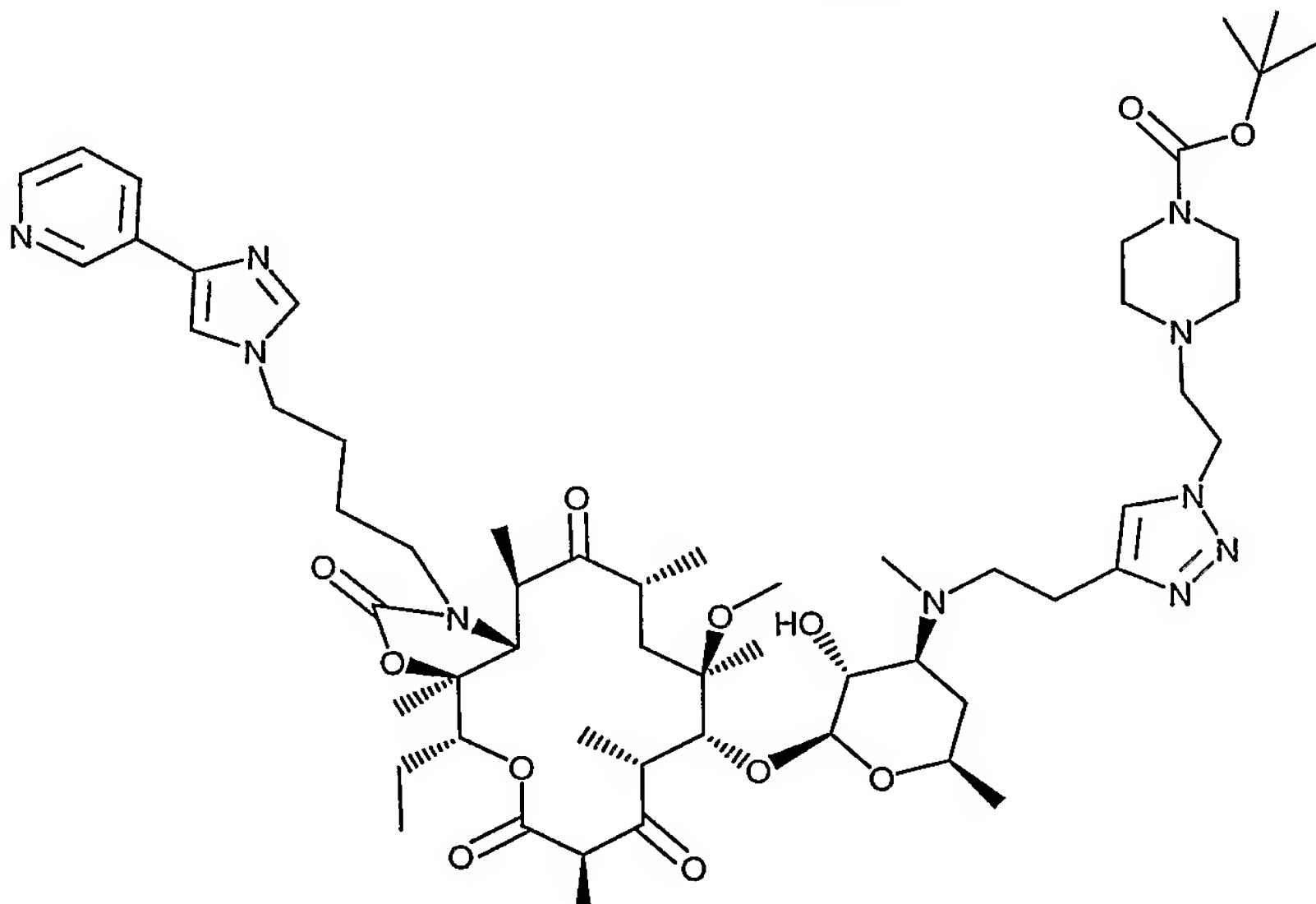
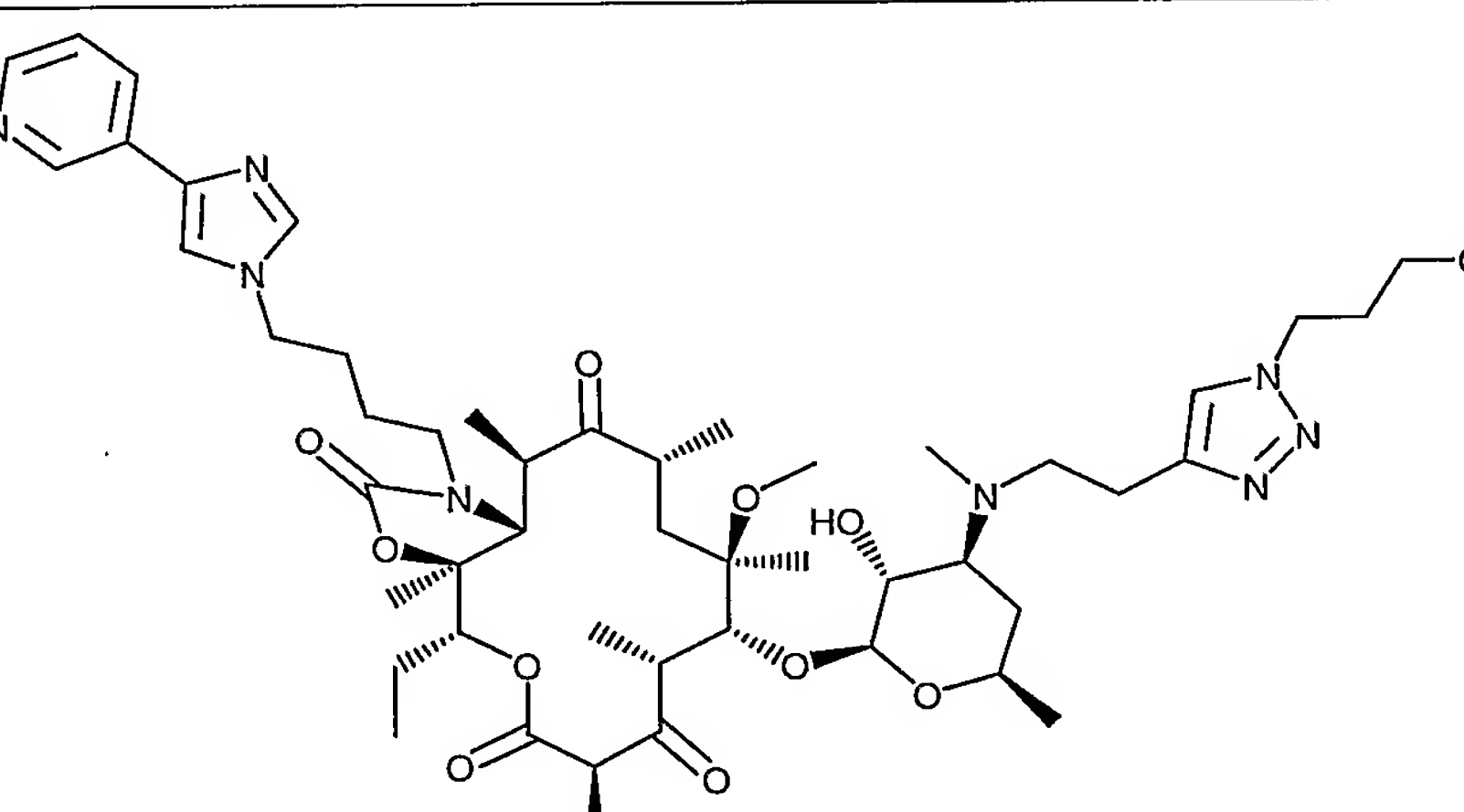
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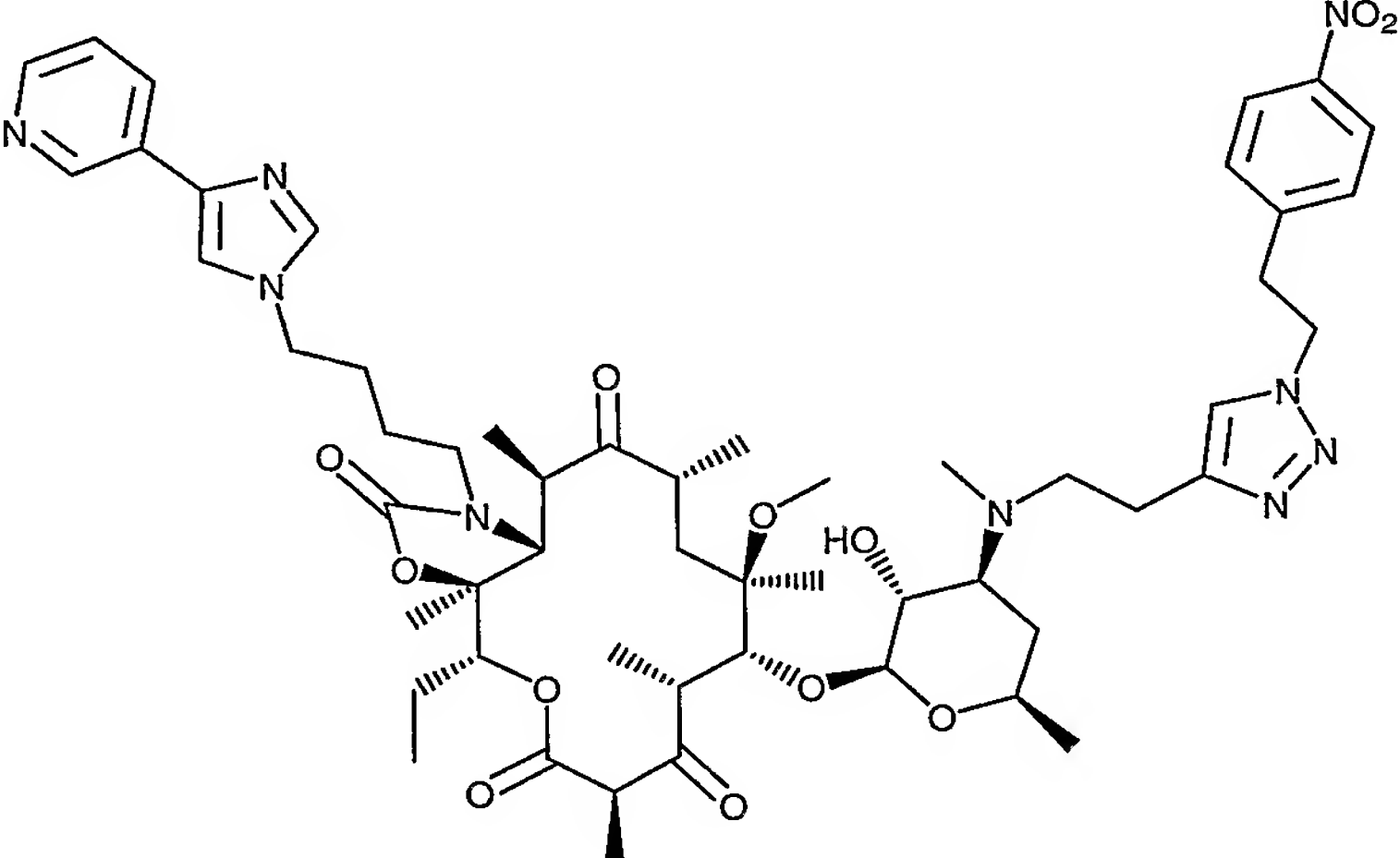
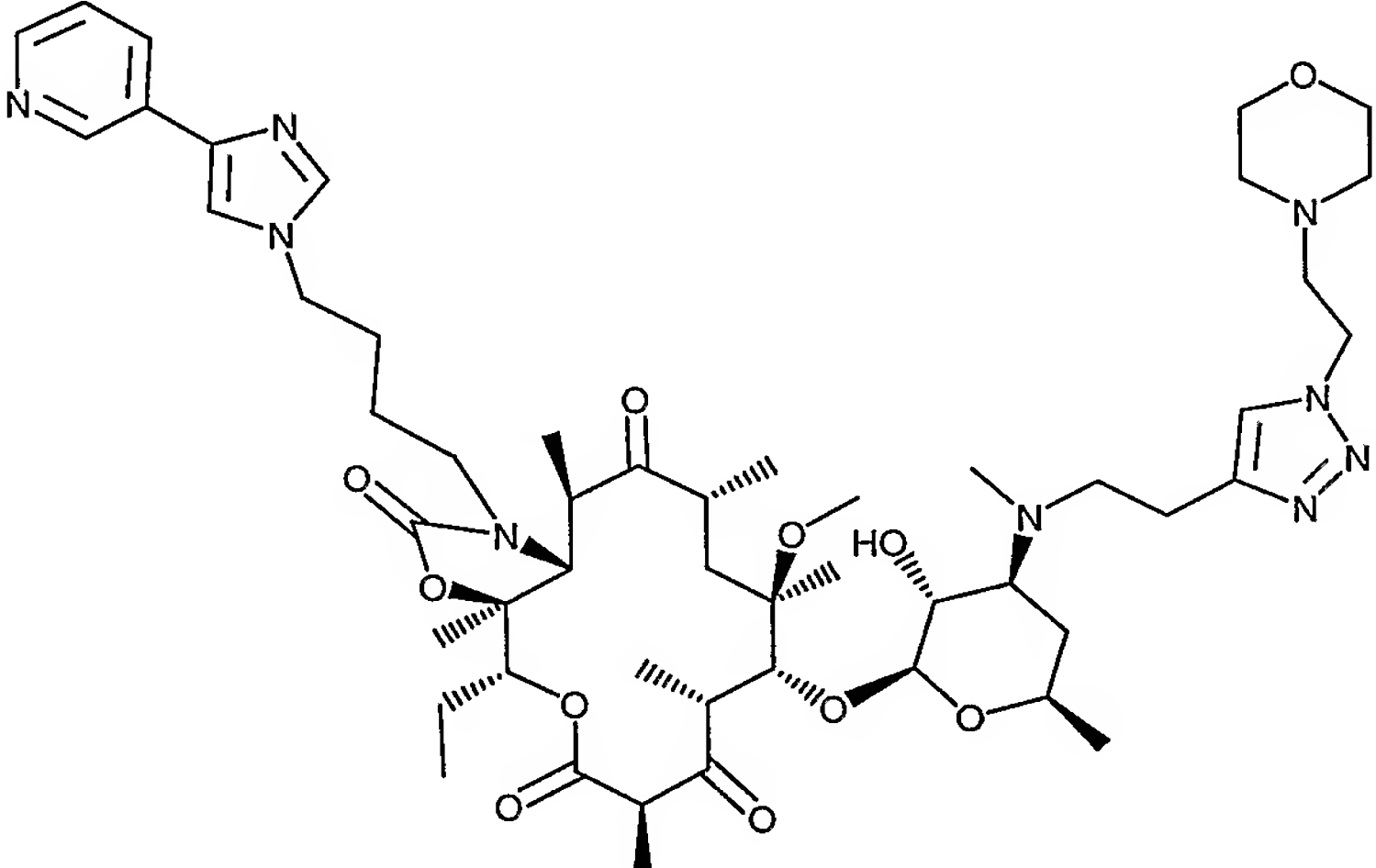
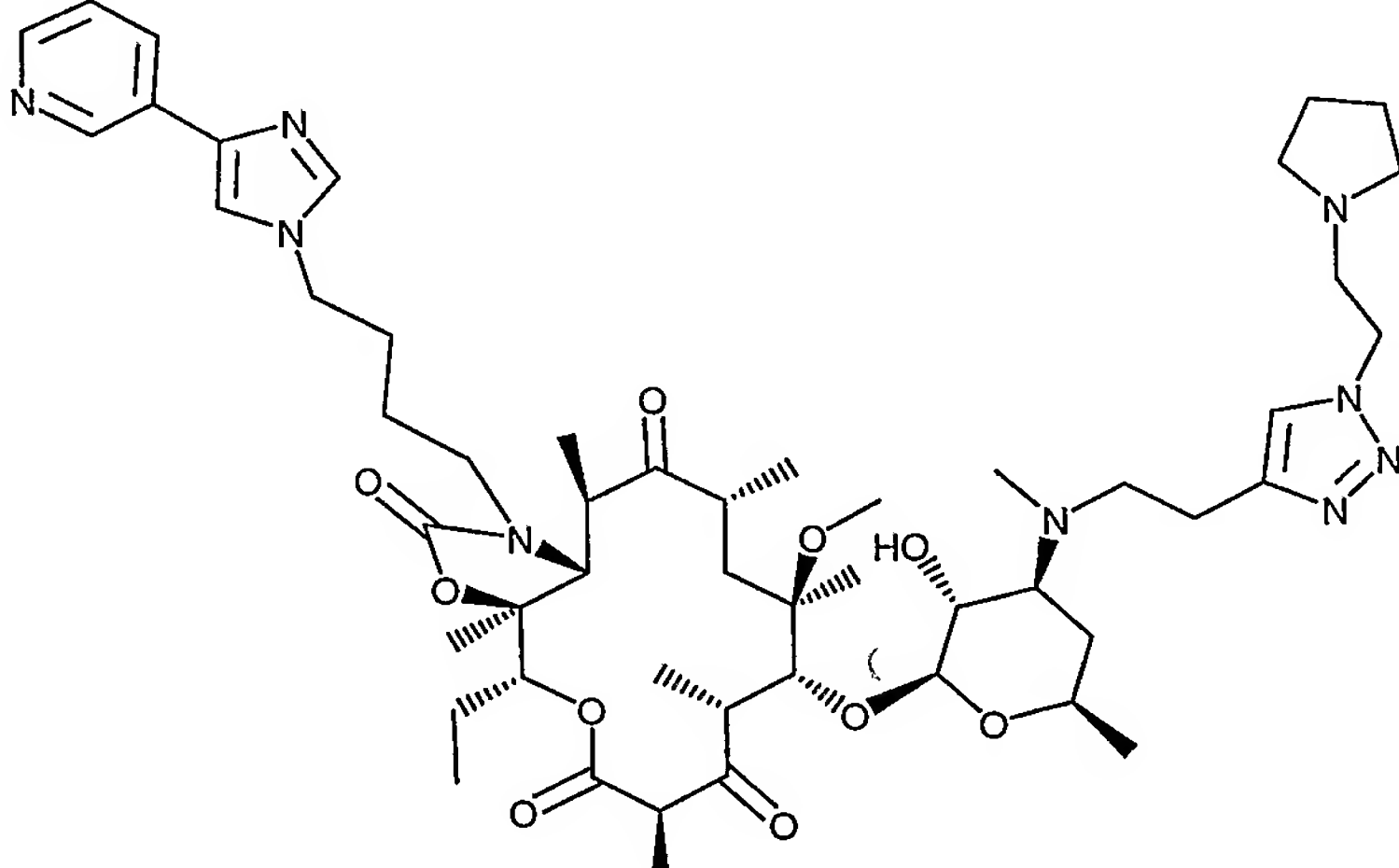
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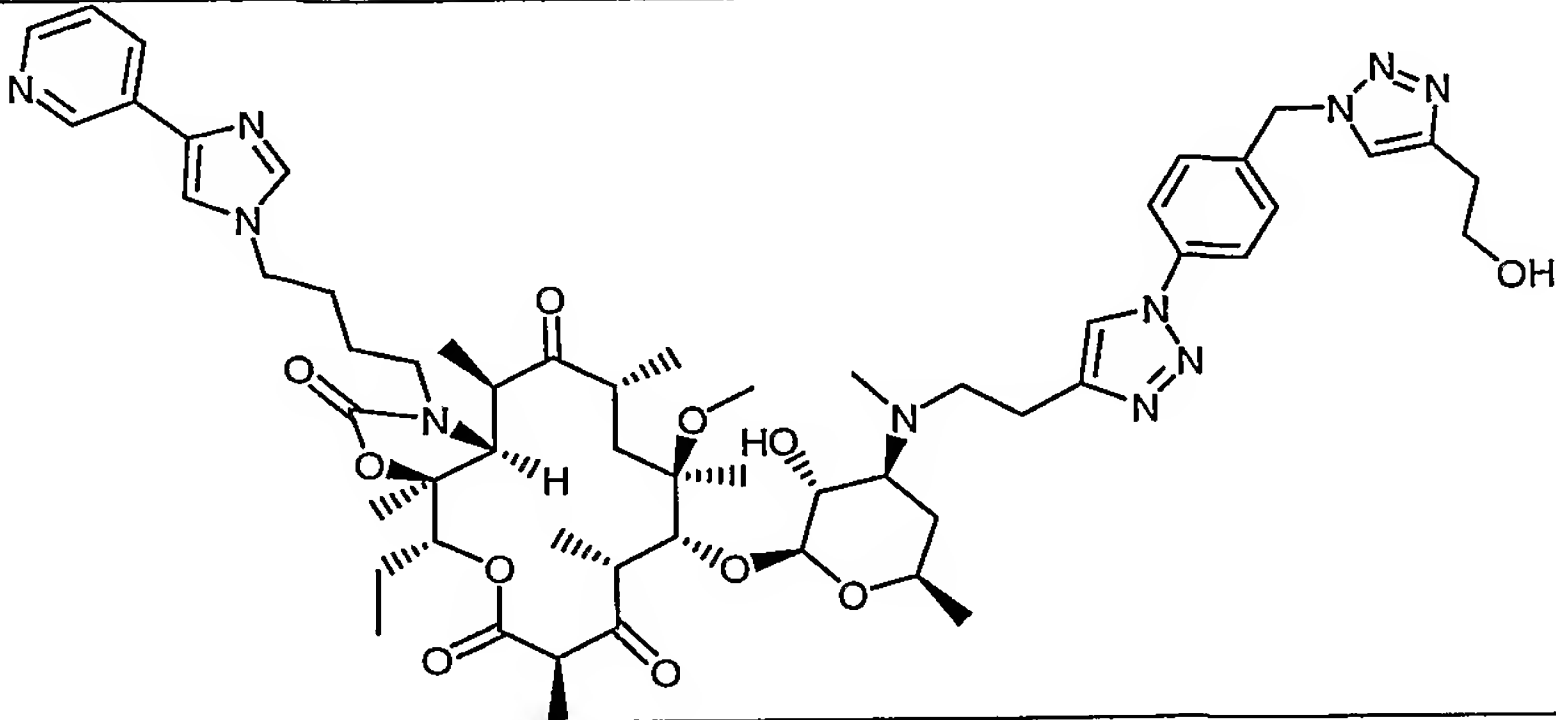
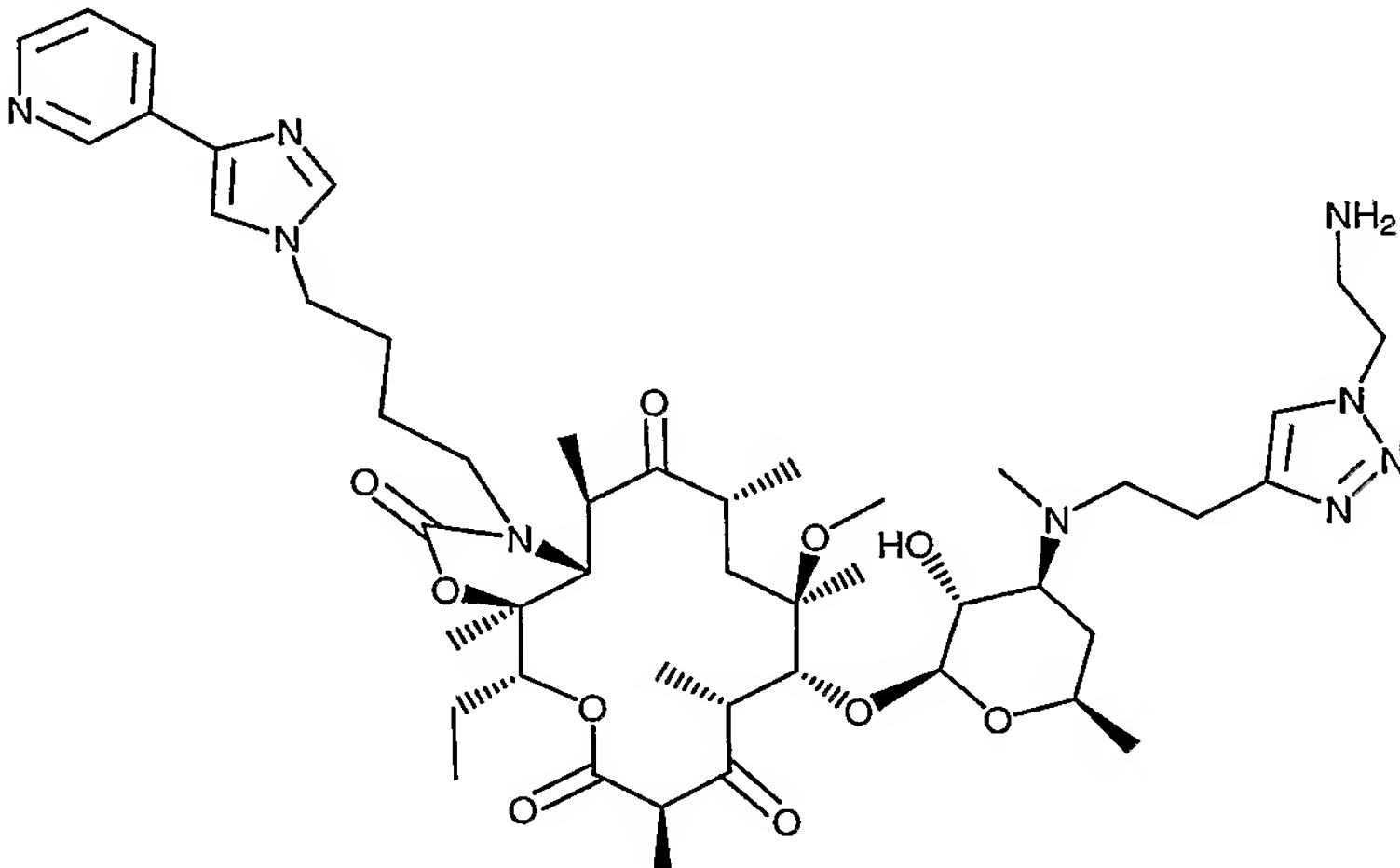
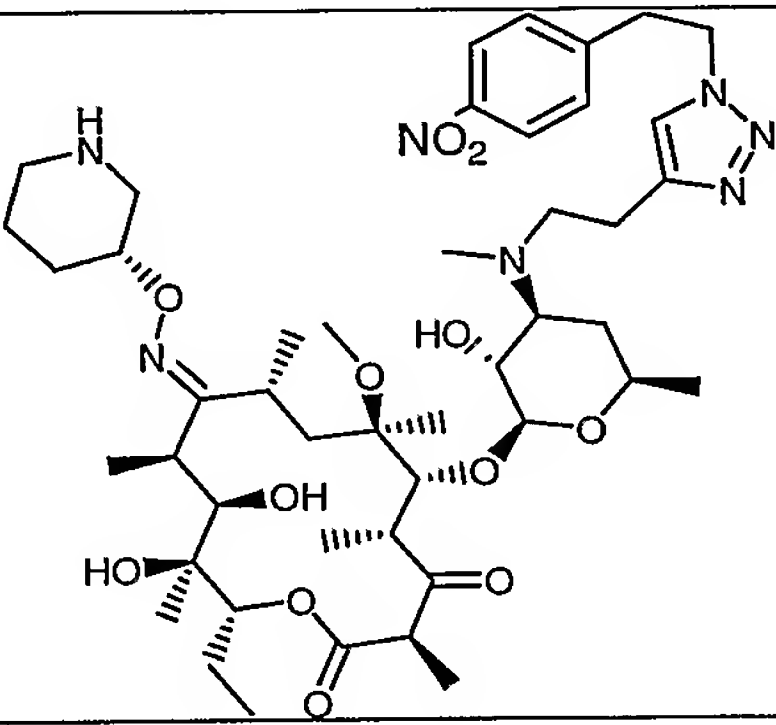
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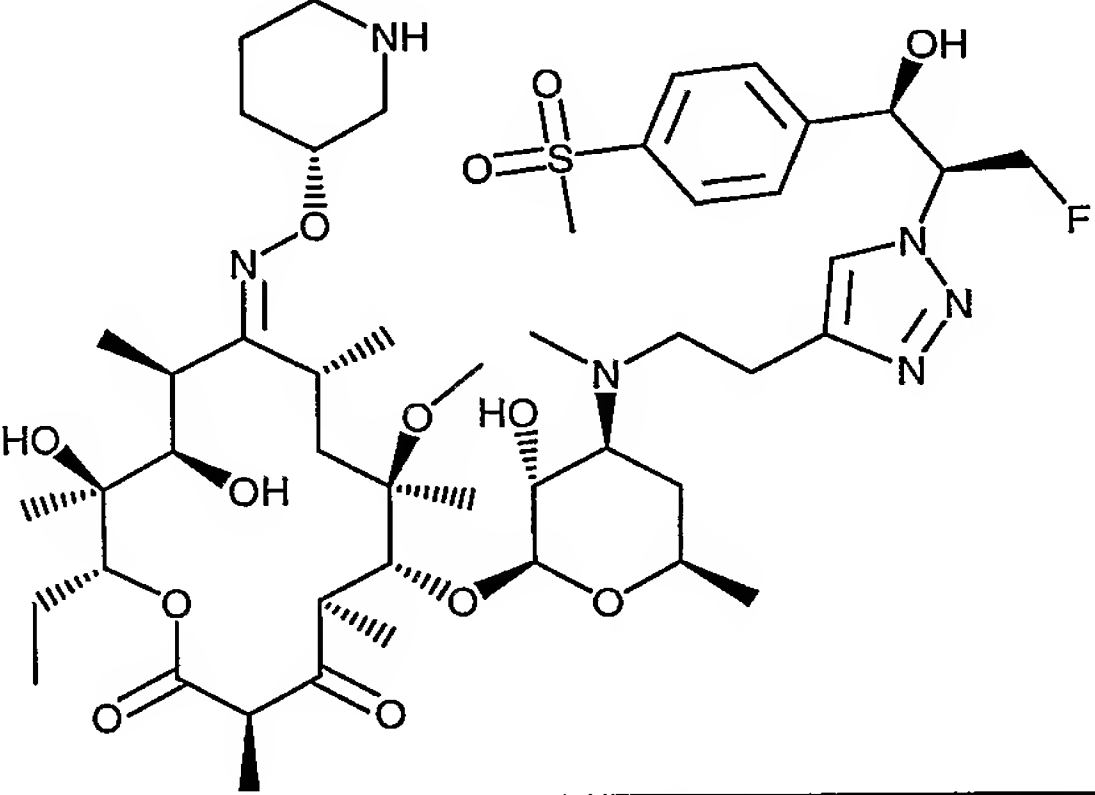
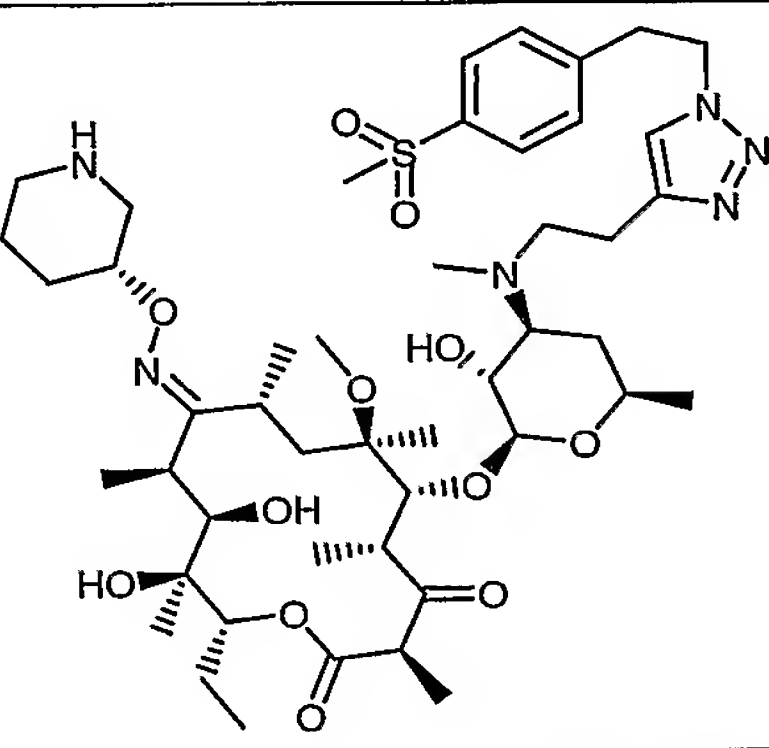
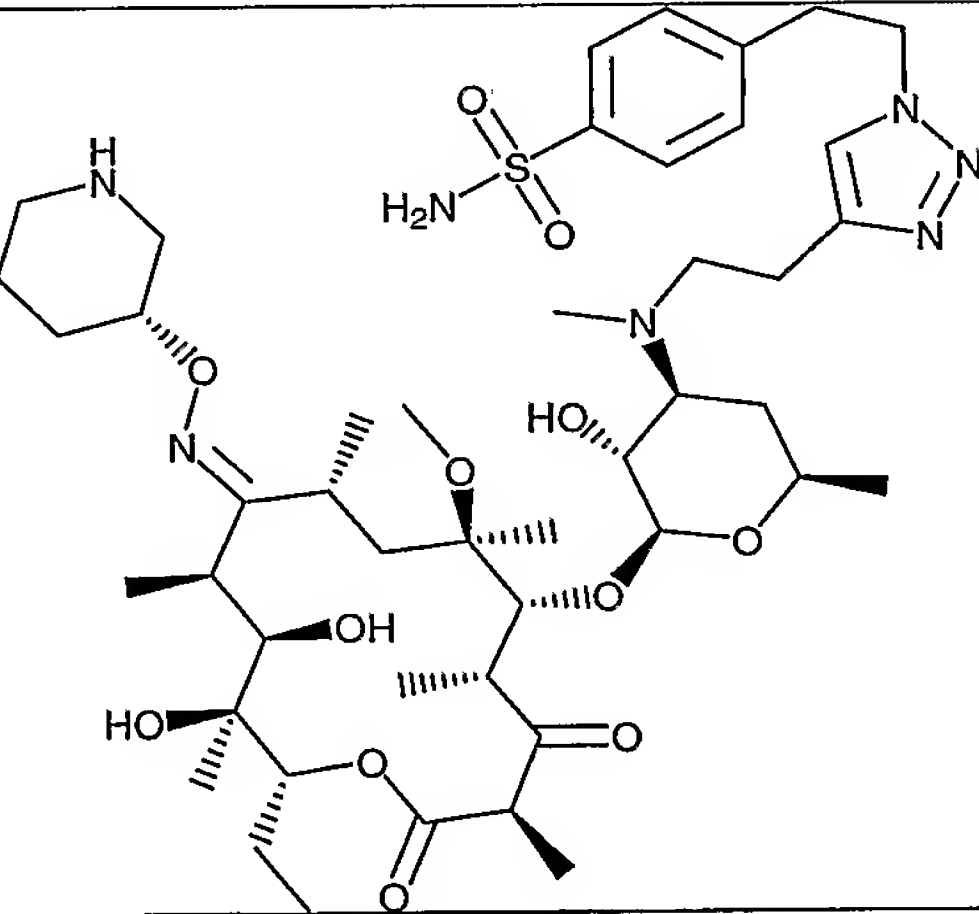
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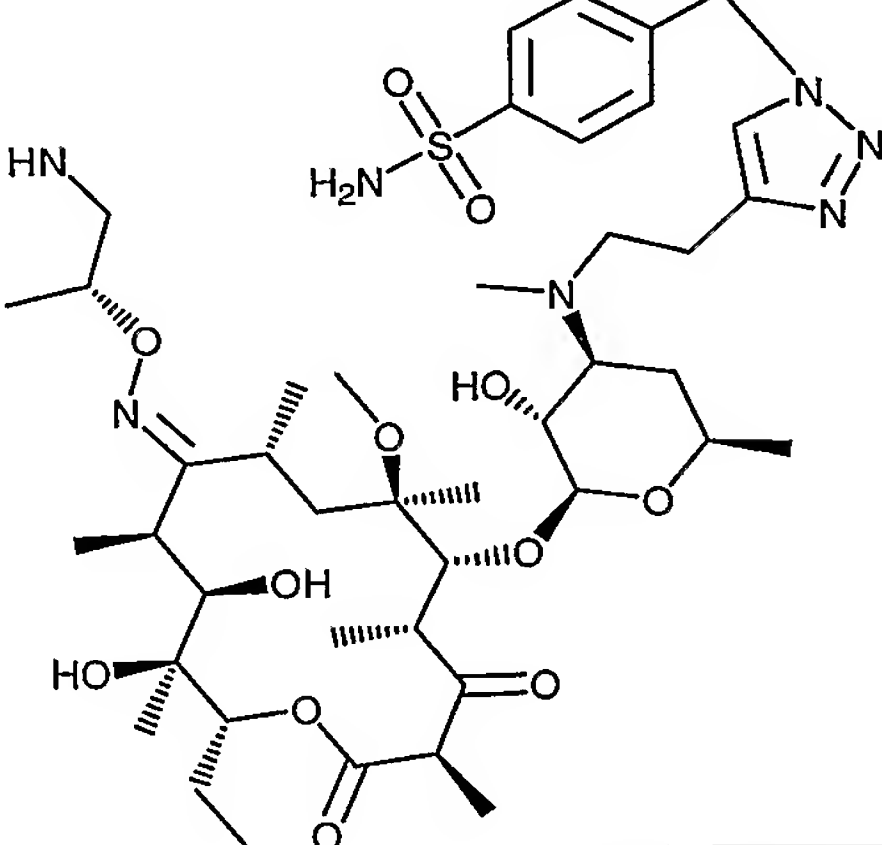
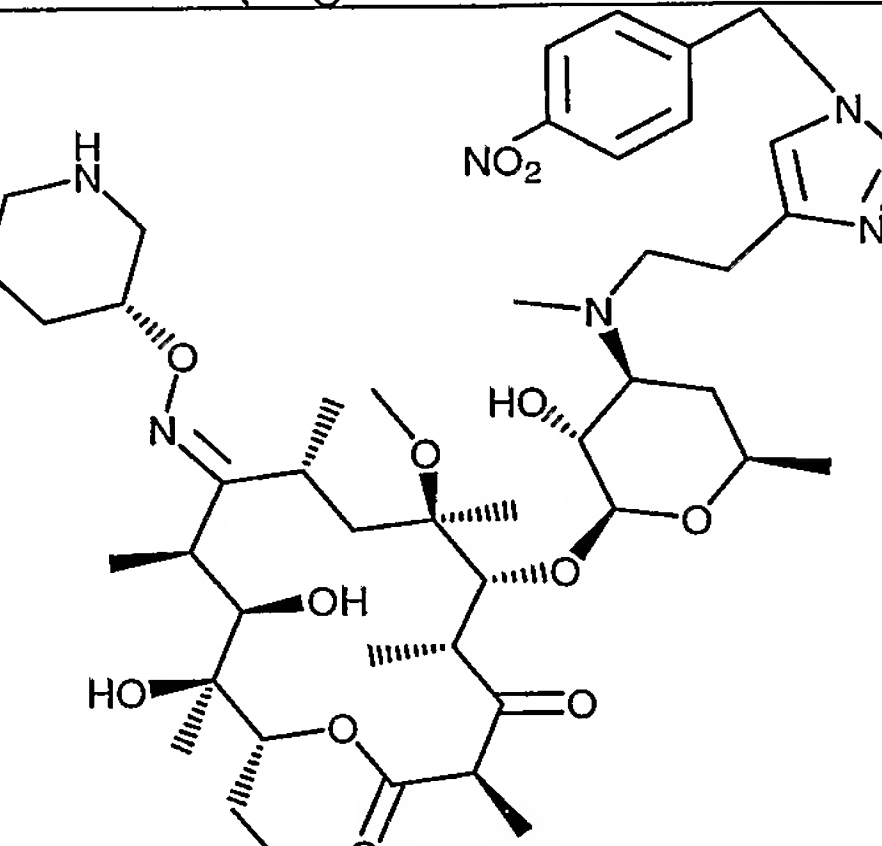
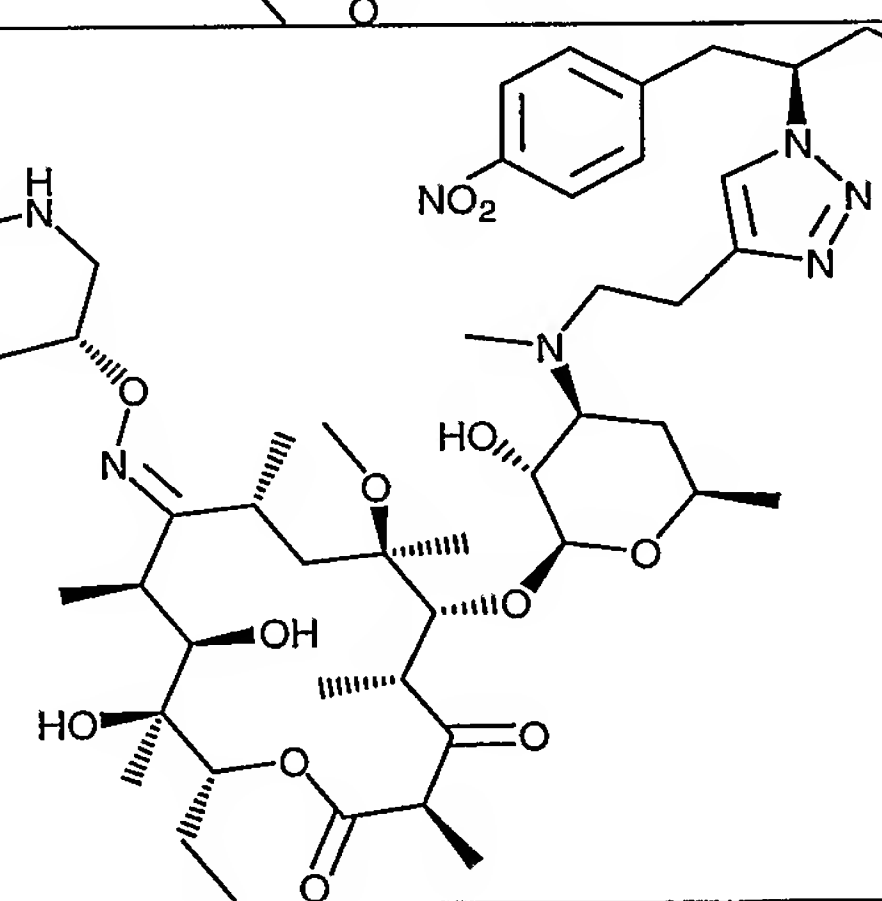
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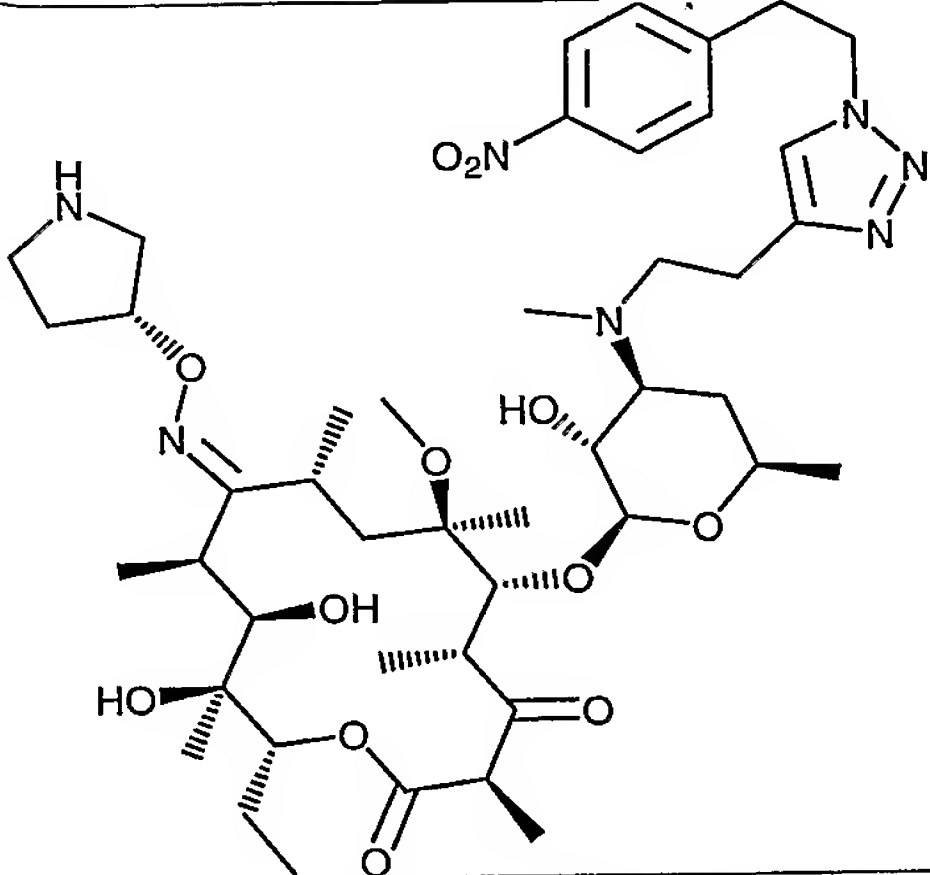
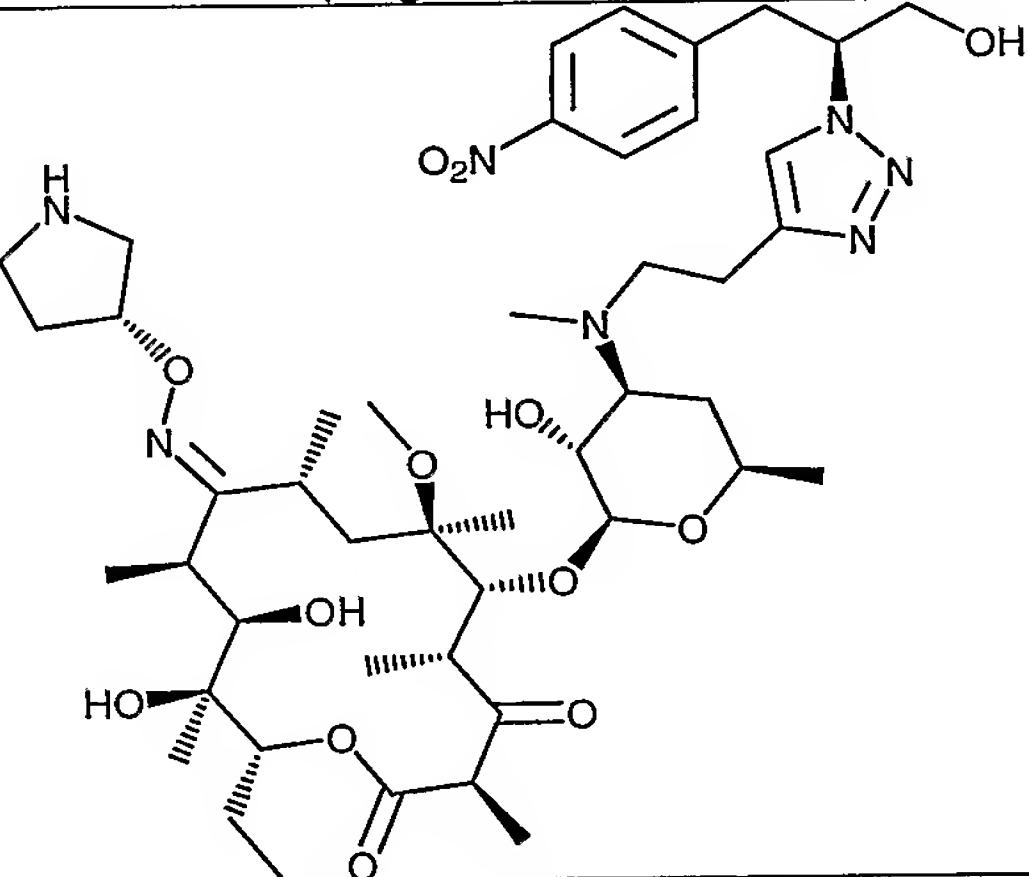
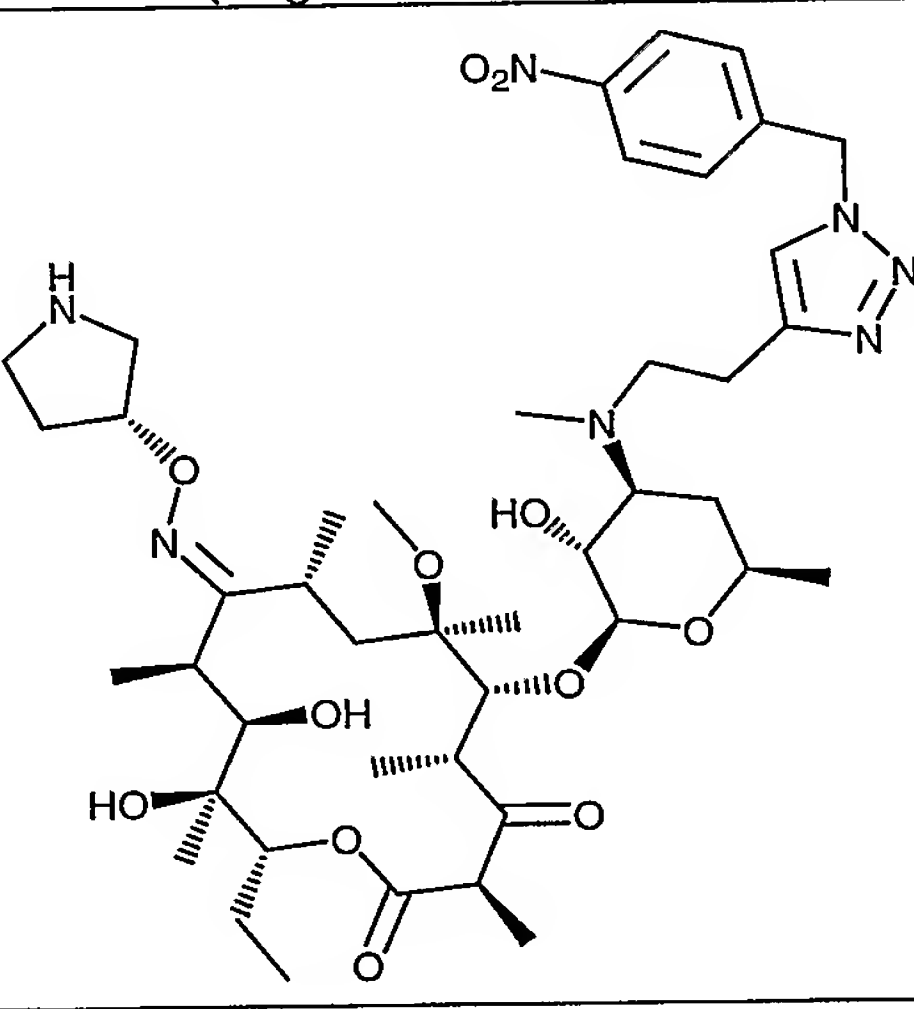
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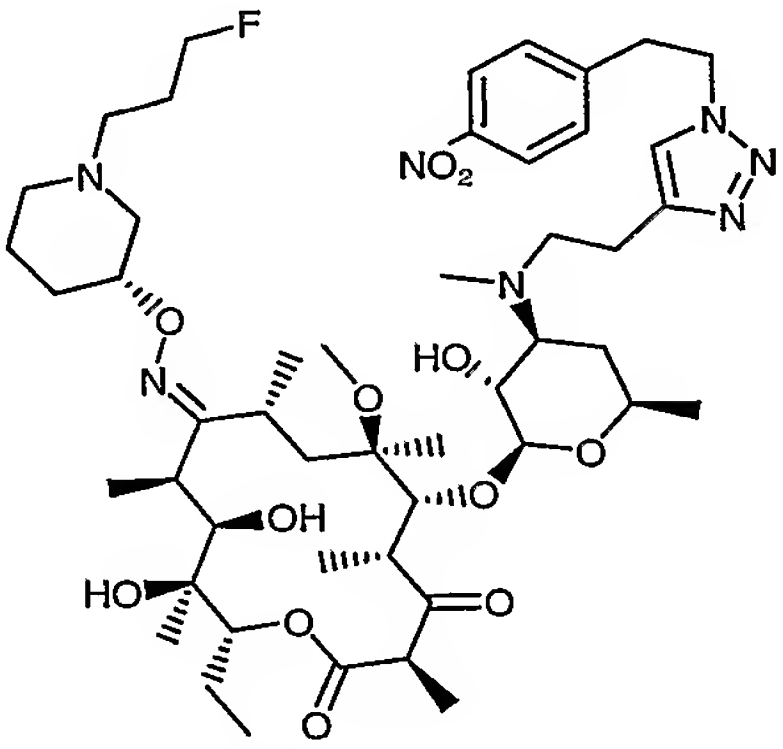
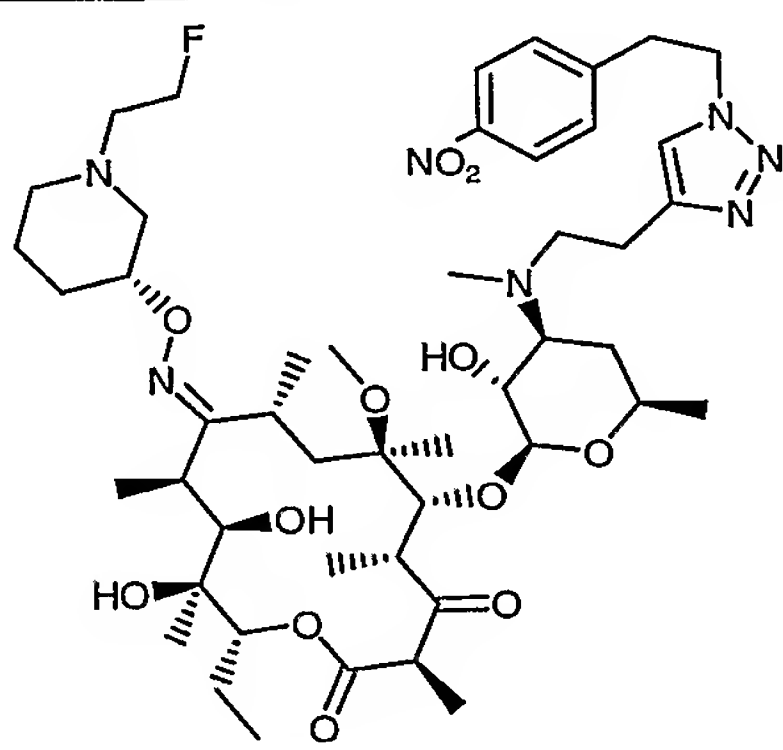
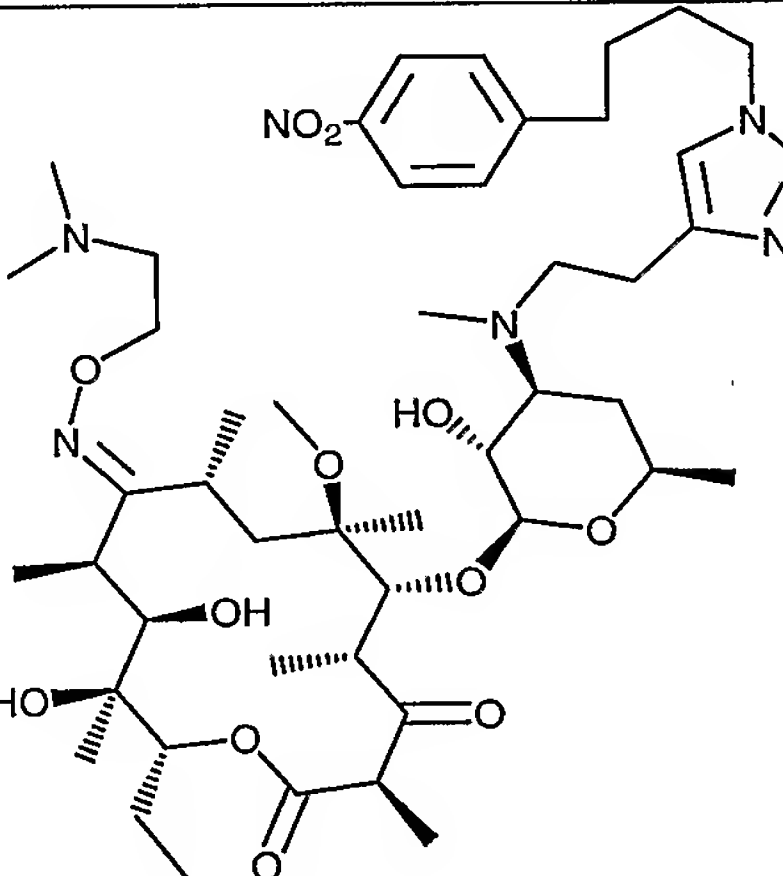
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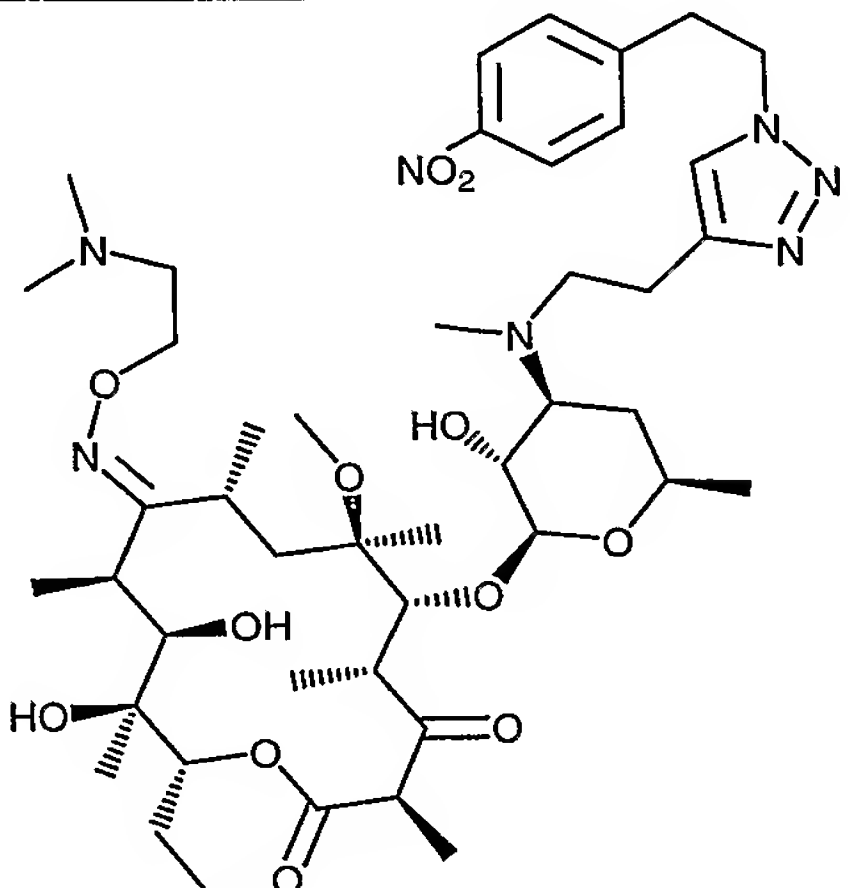
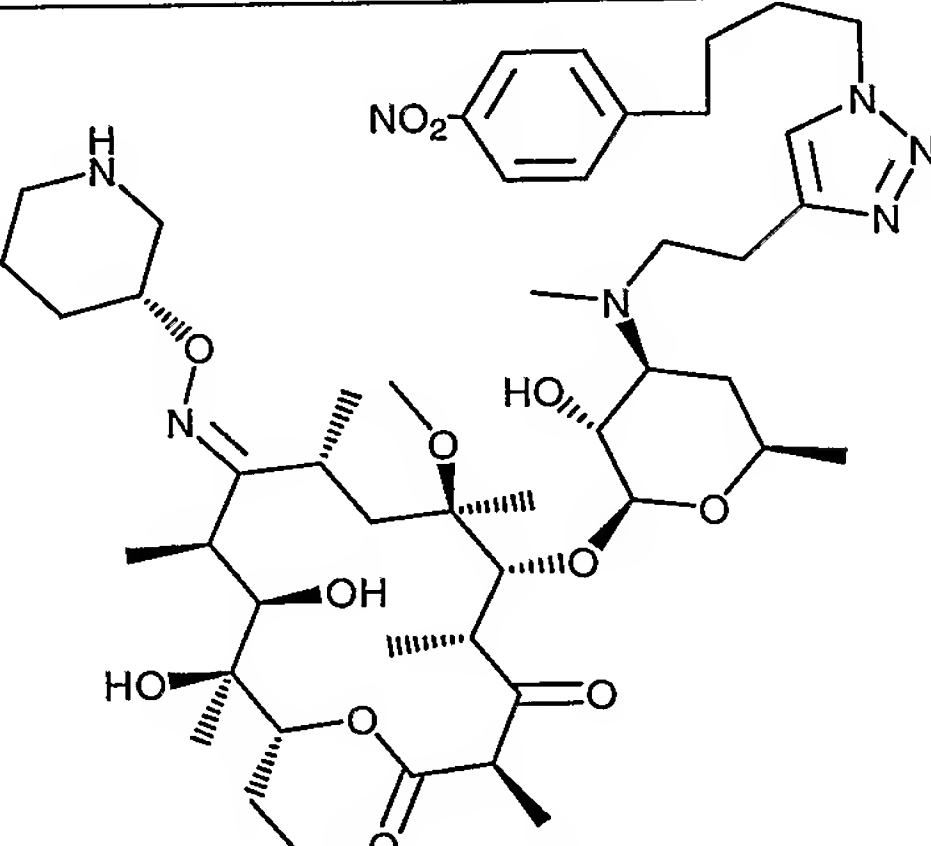
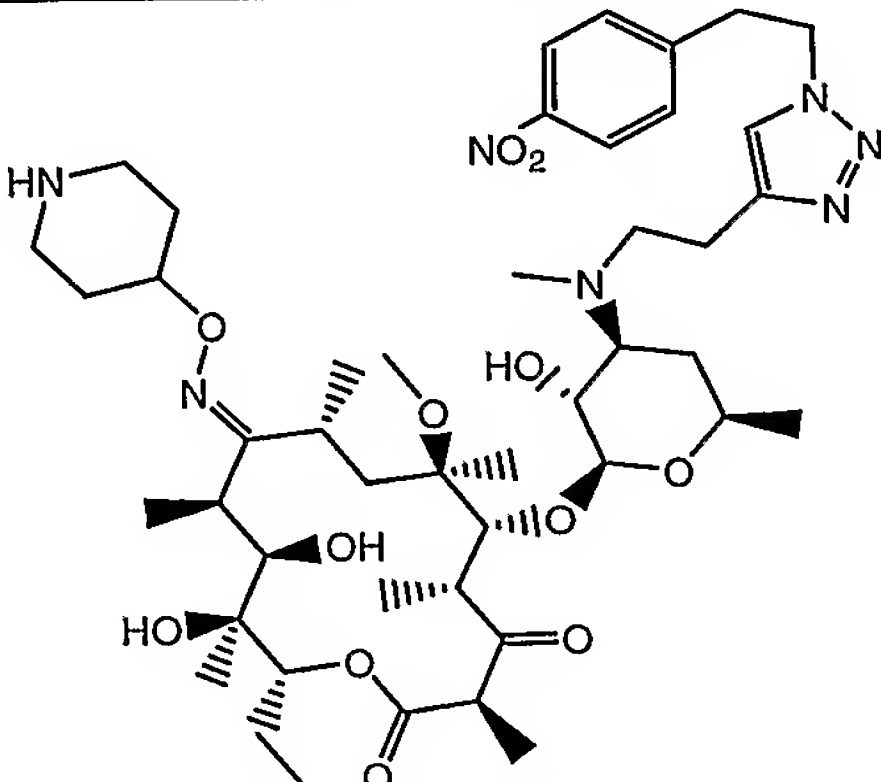
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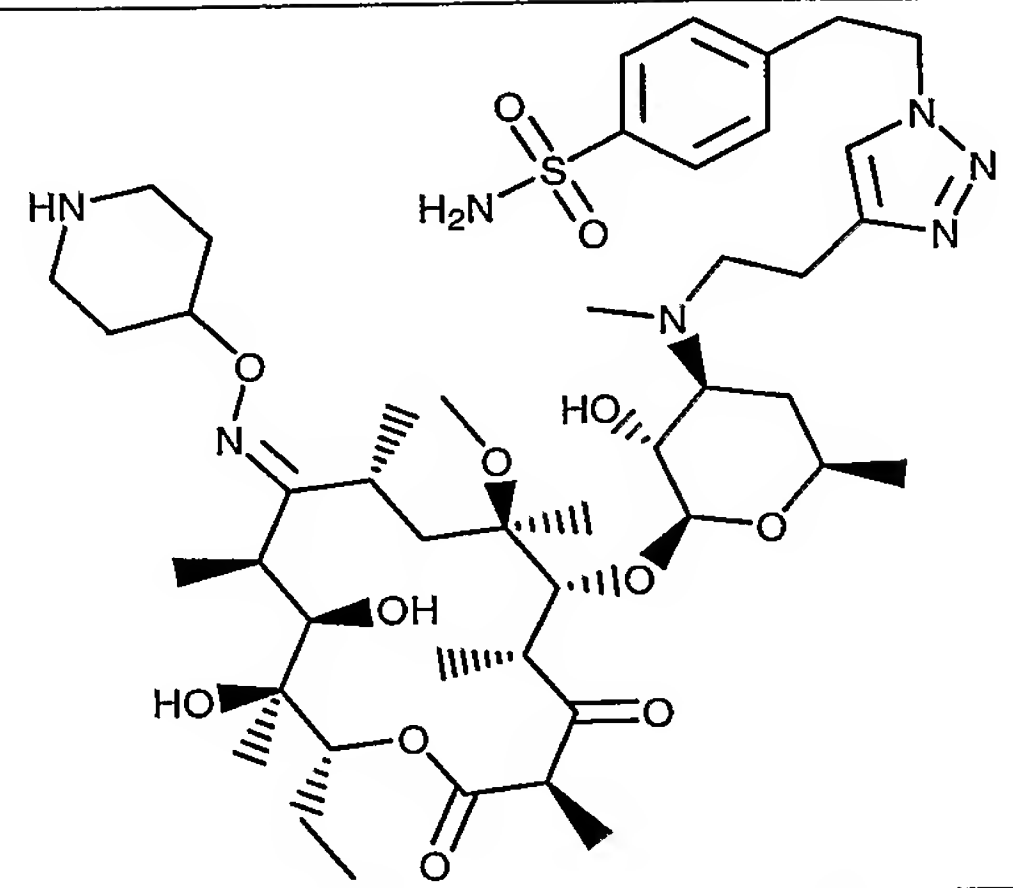
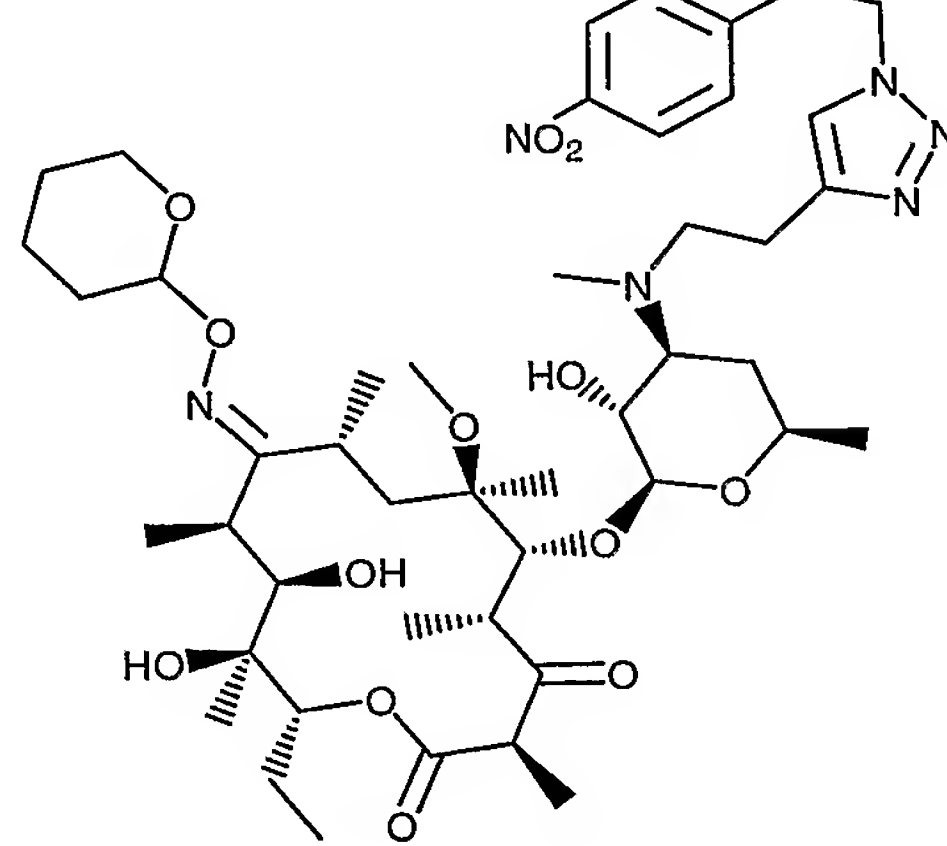
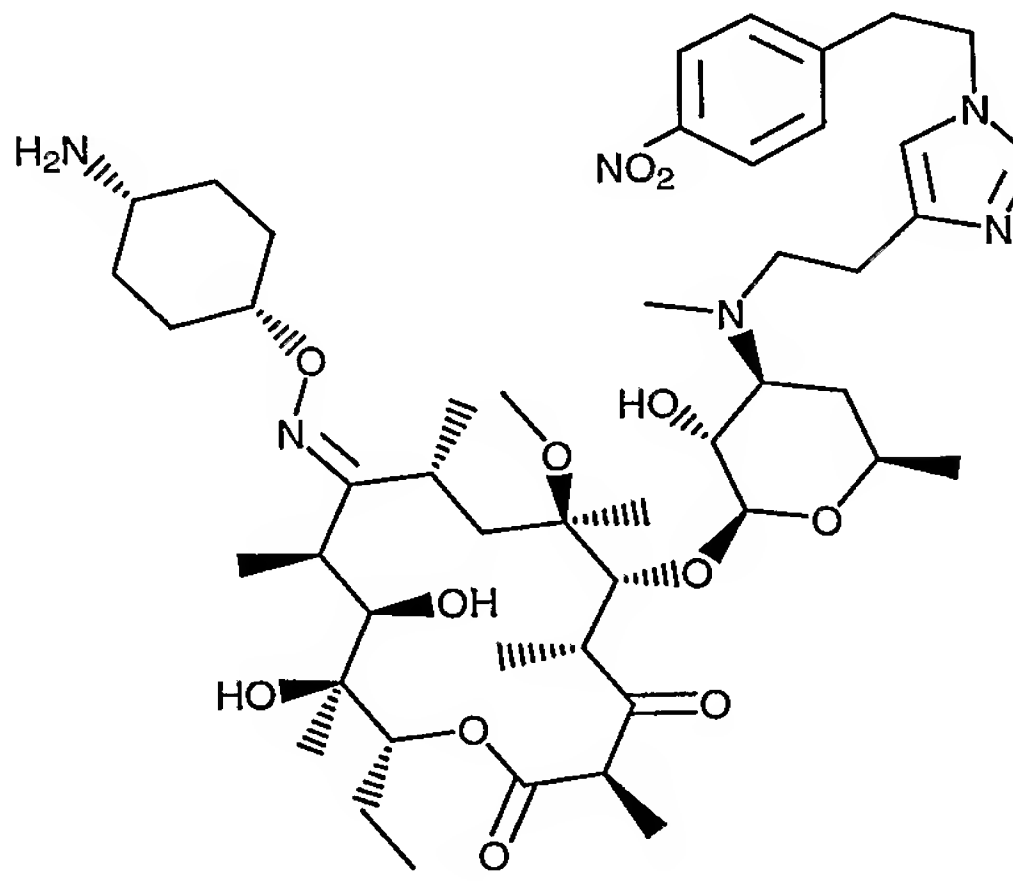
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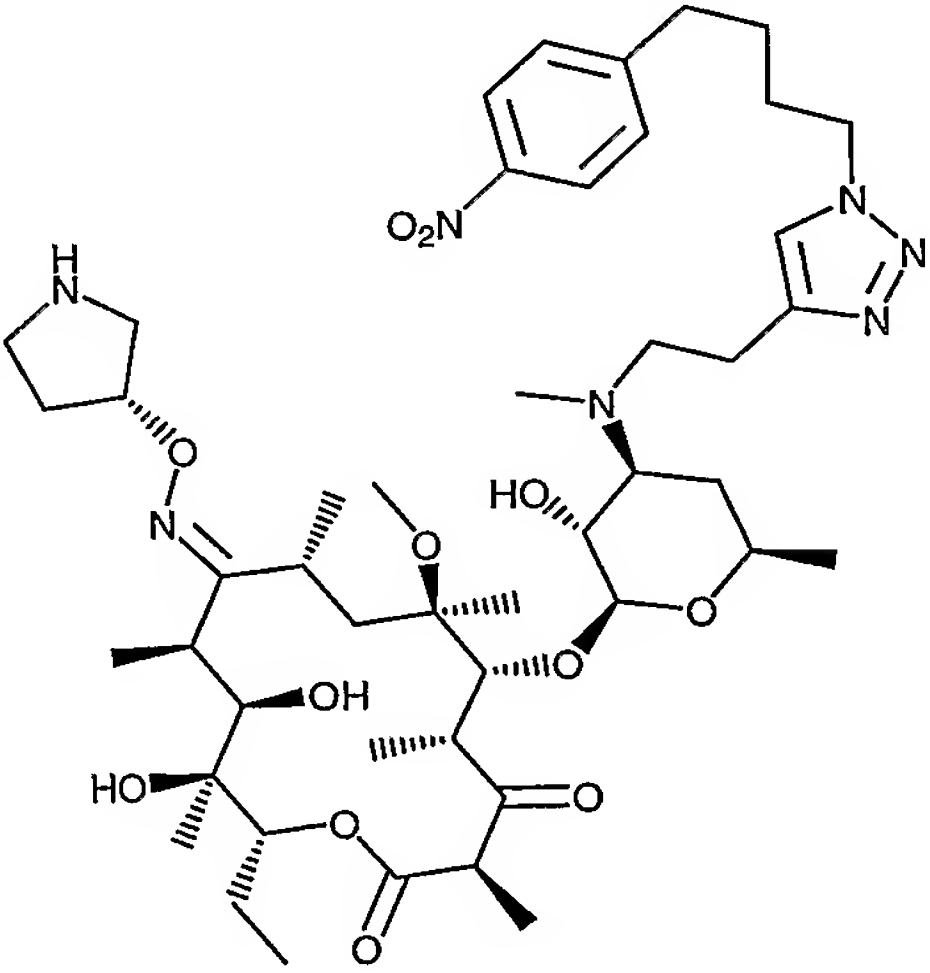
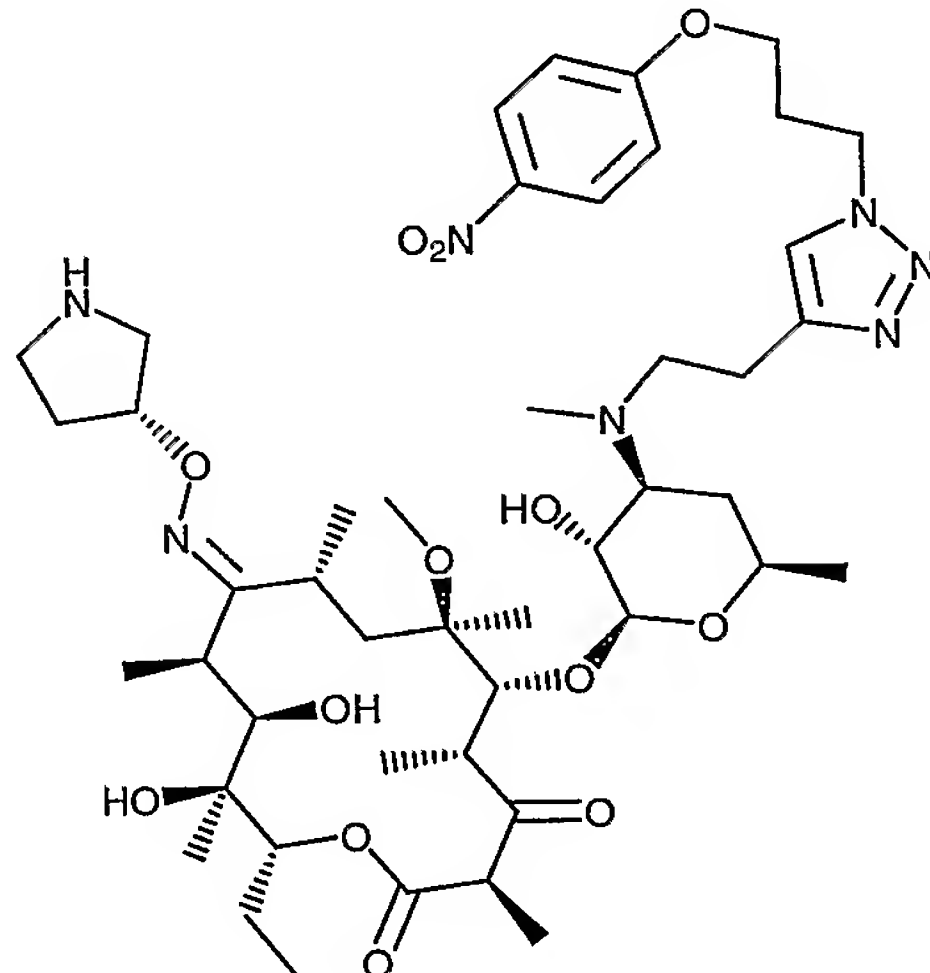
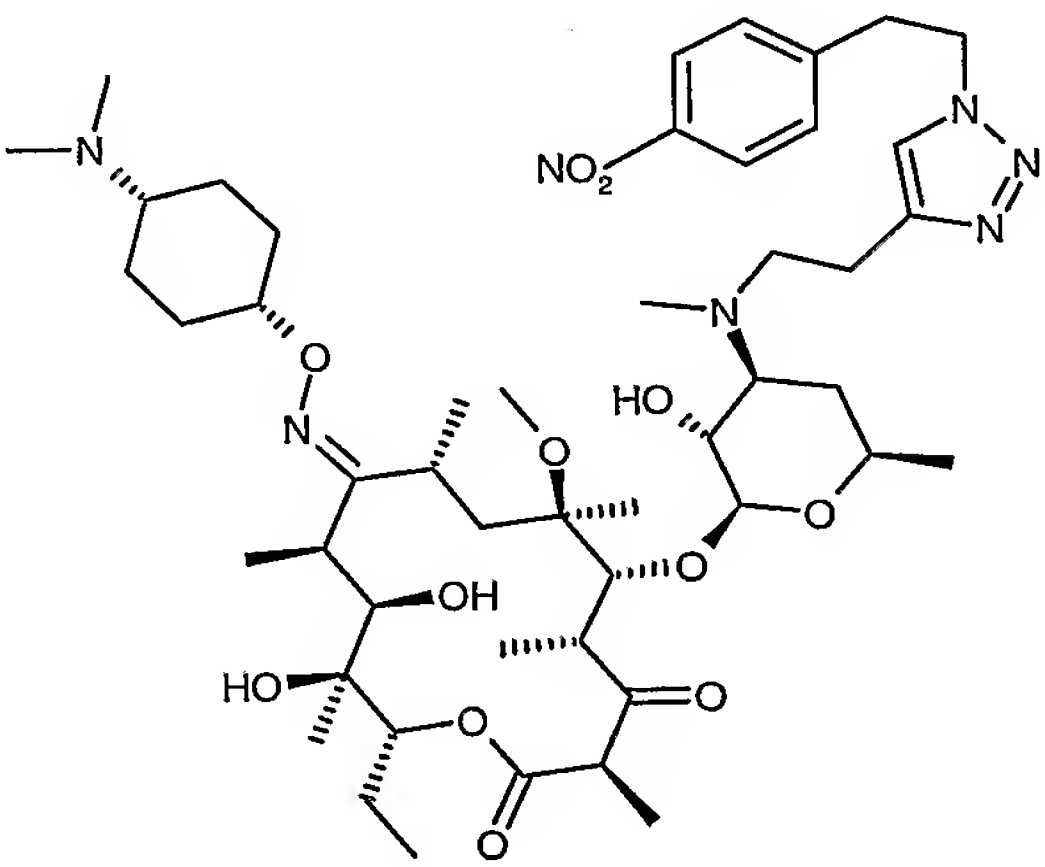
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438	 <p>Chemical structure 438: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a carbonyl group. It is substituted with a dimethylaminoethoxy group, a 4-nitrophenyl group, and a 1,2,4-triazole ring.</p>
439	 <p>Chemical structure 439: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a carbonyl group. It is substituted with a piperidinomethoxy group, a 4-nitrophenyl group, and a 1,2,4-triazole ring.</p>
440	 <p>Chemical structure 440: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a carbonyl group. It is substituted with a piperidinomethoxy group, a 4-nitrophenyl group, and a 1,2,4-triazole ring.</p>

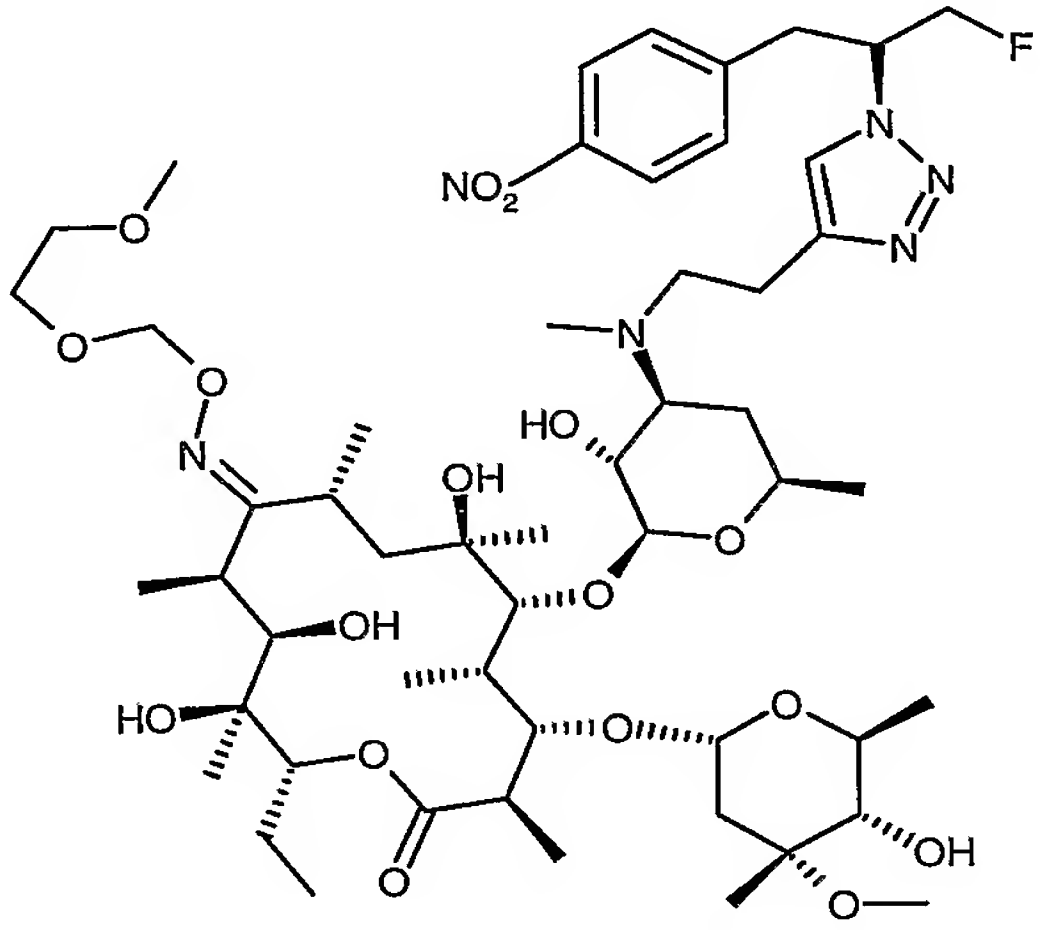
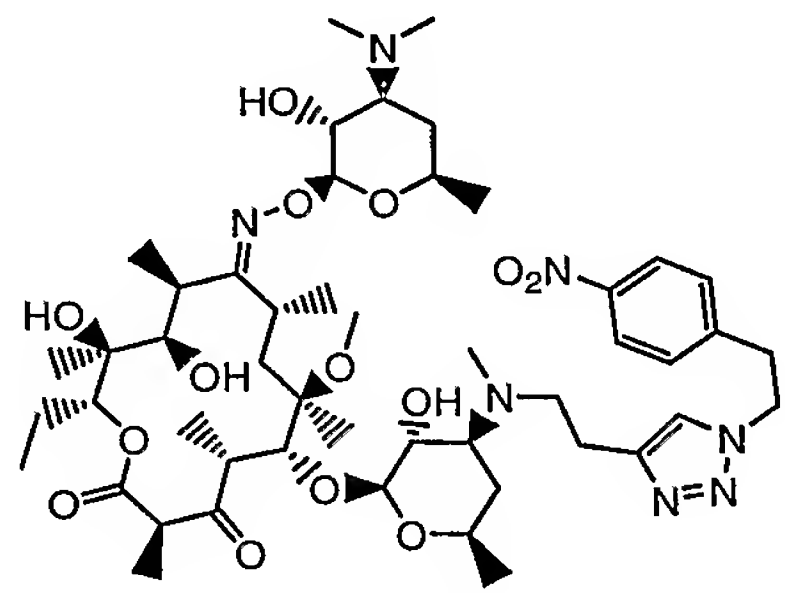
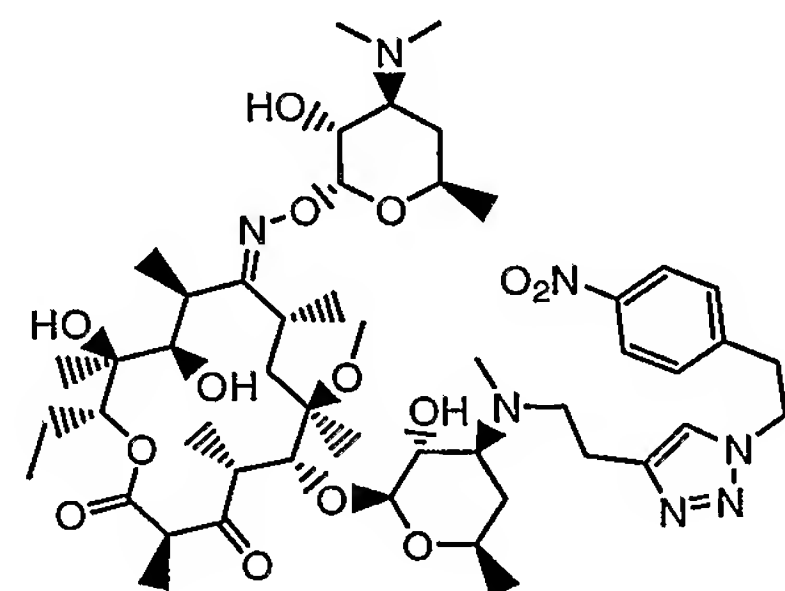
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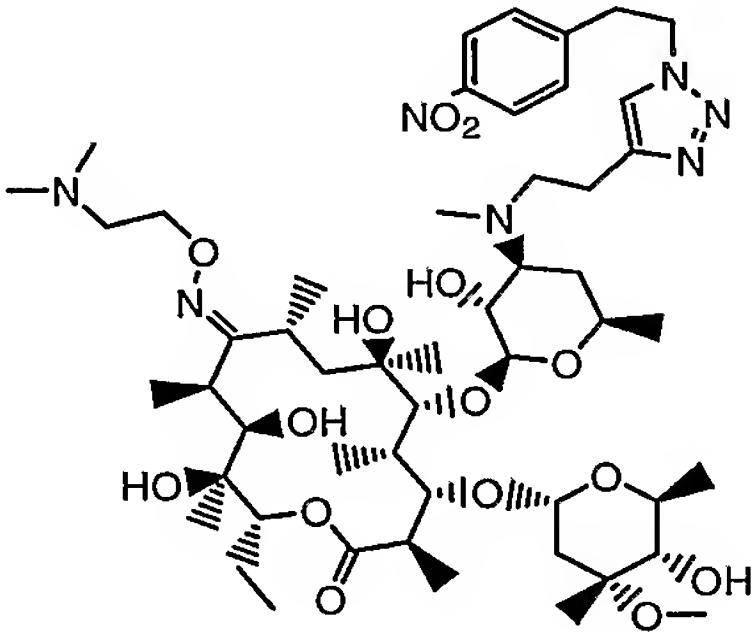
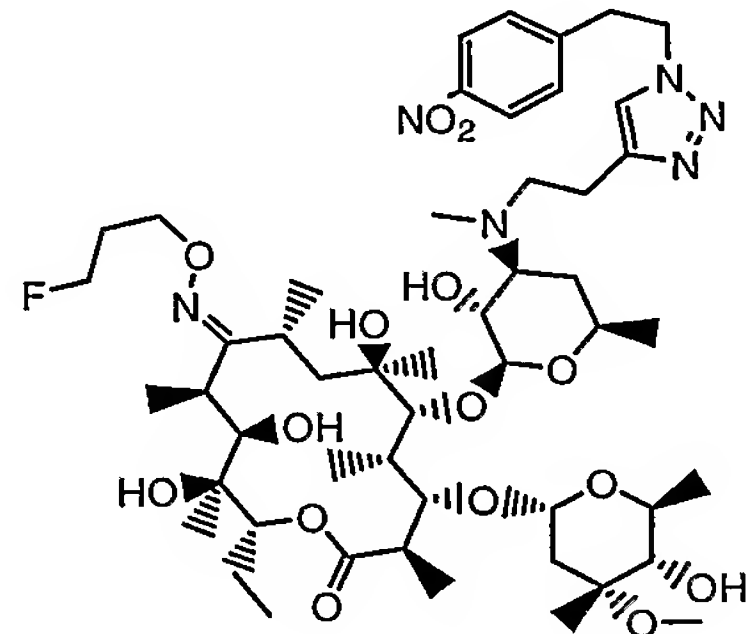
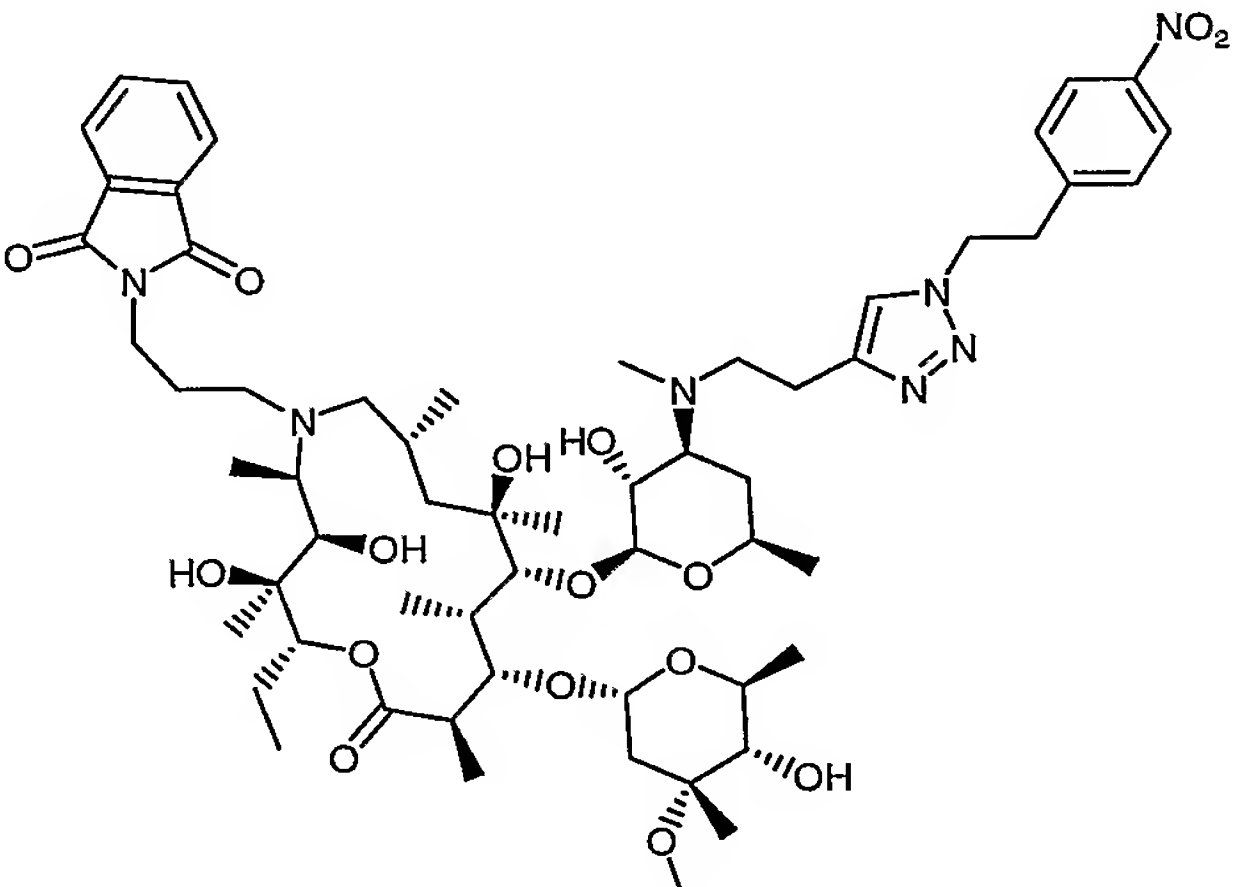
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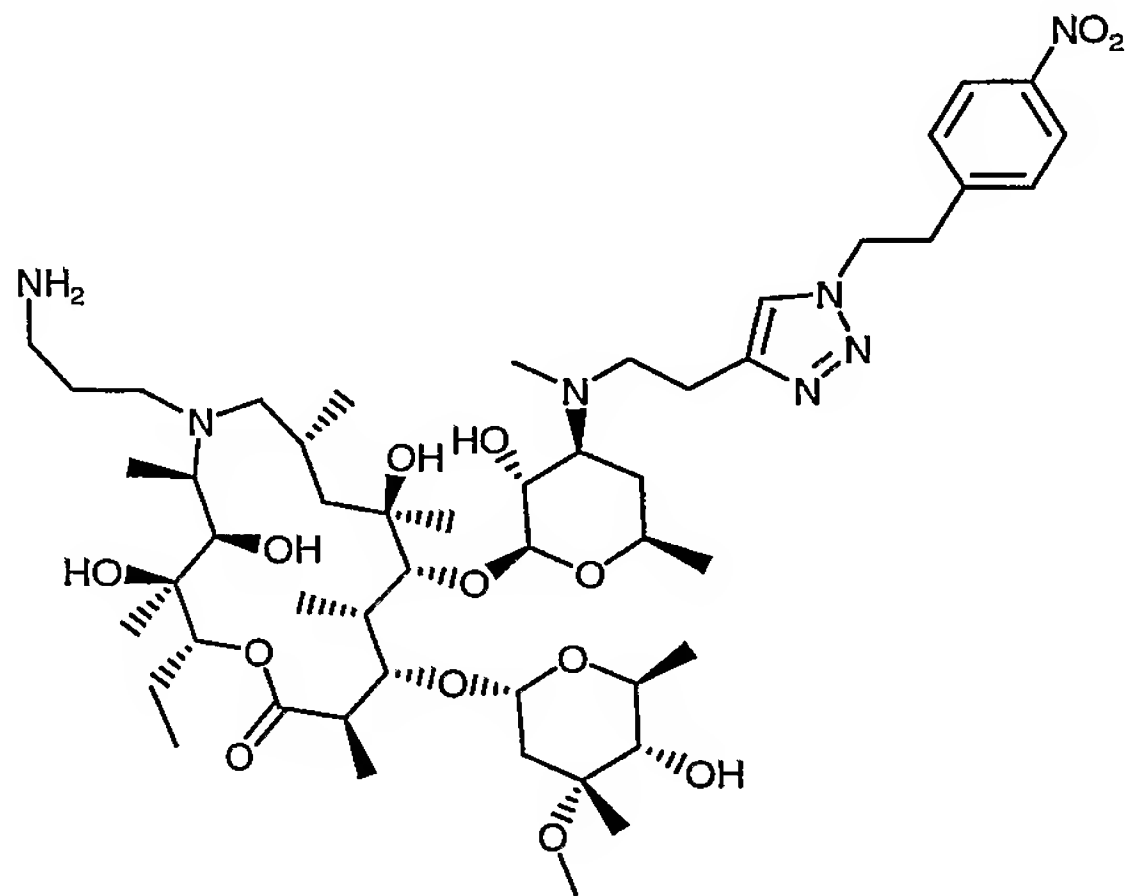
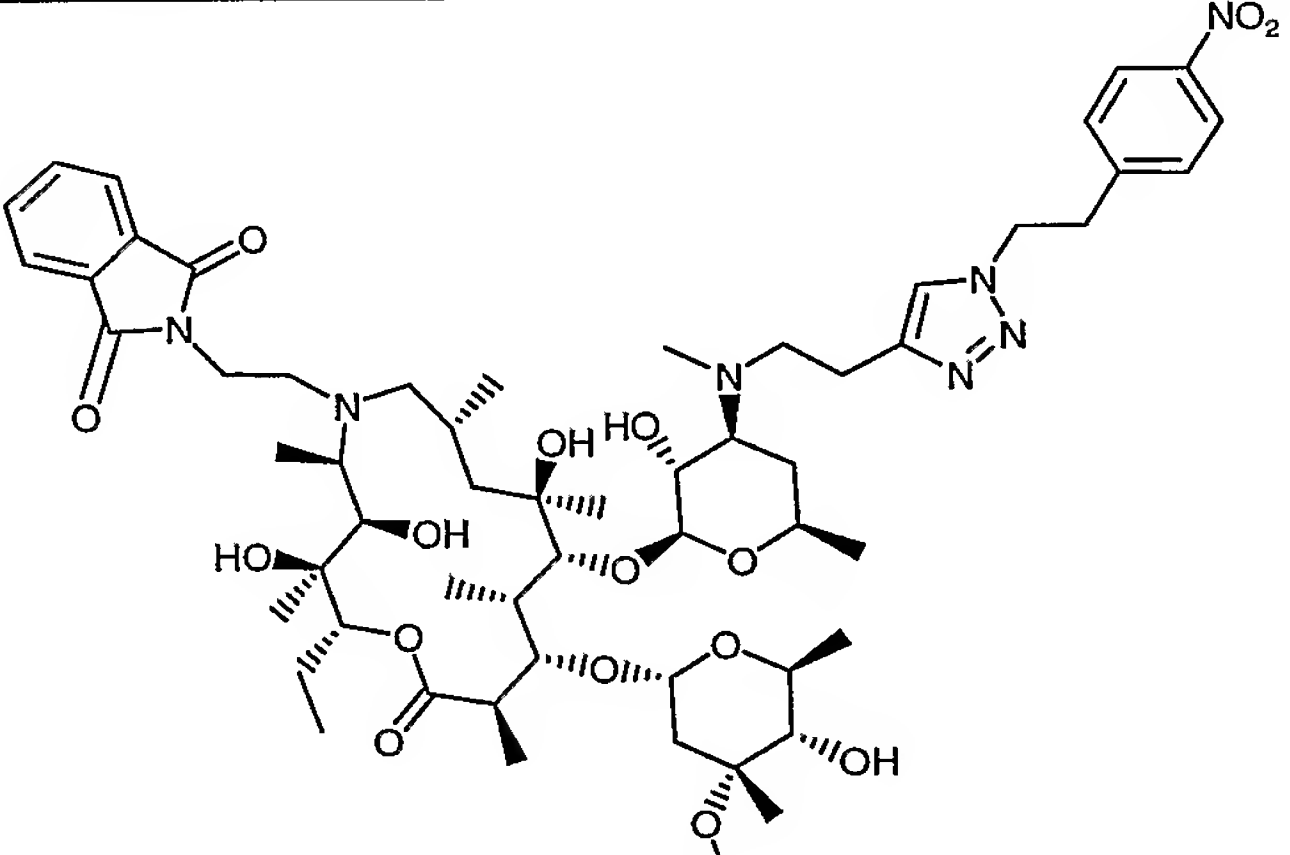
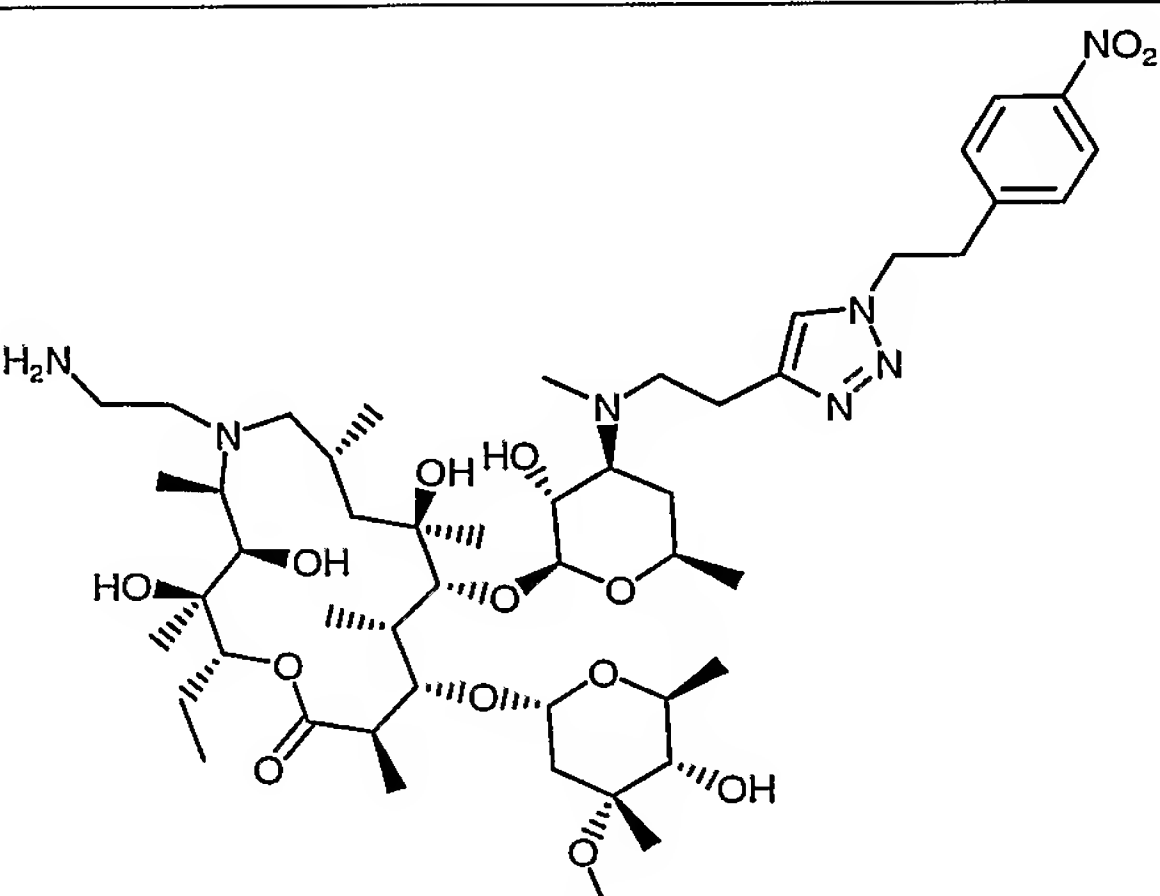
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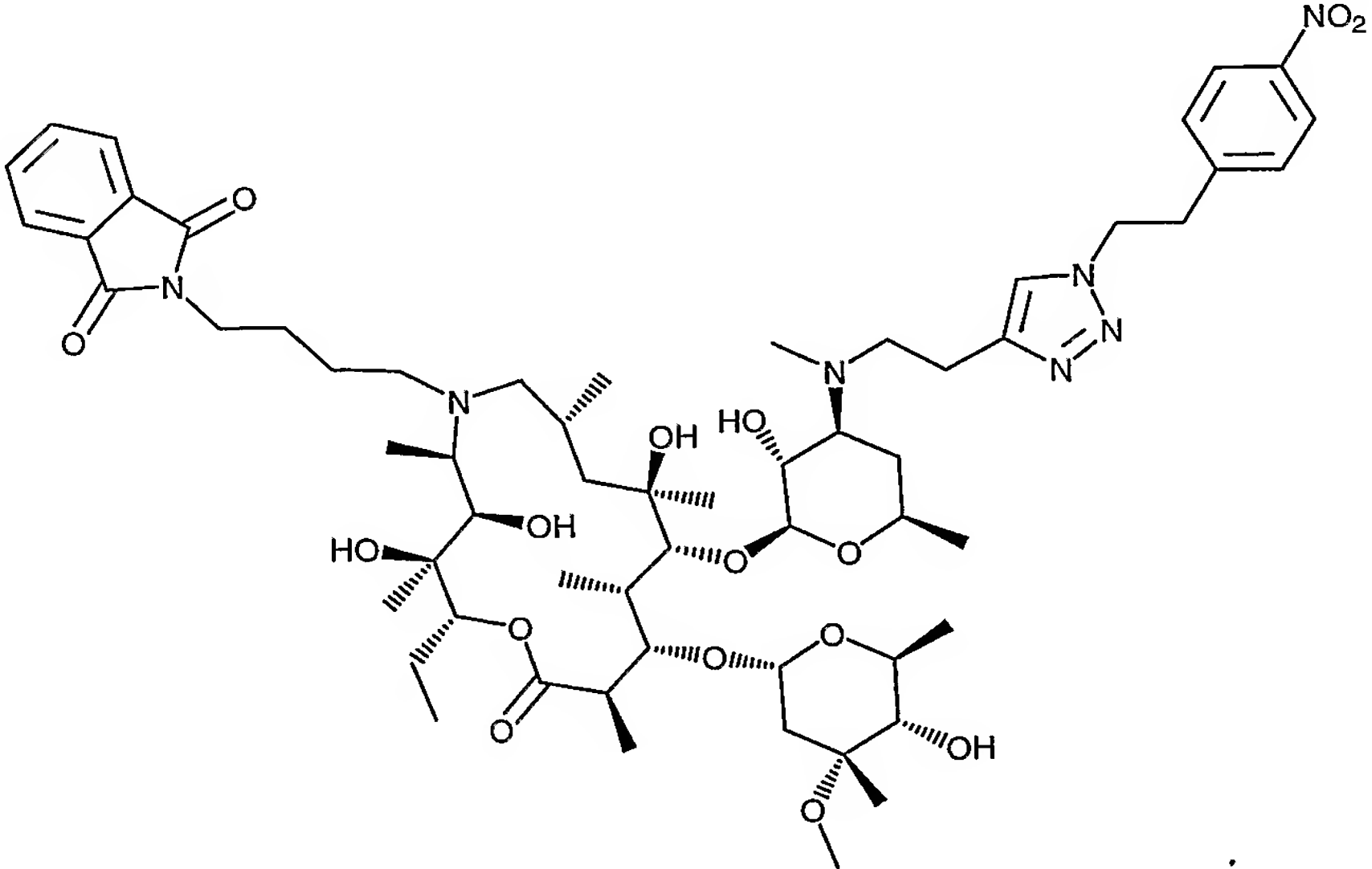
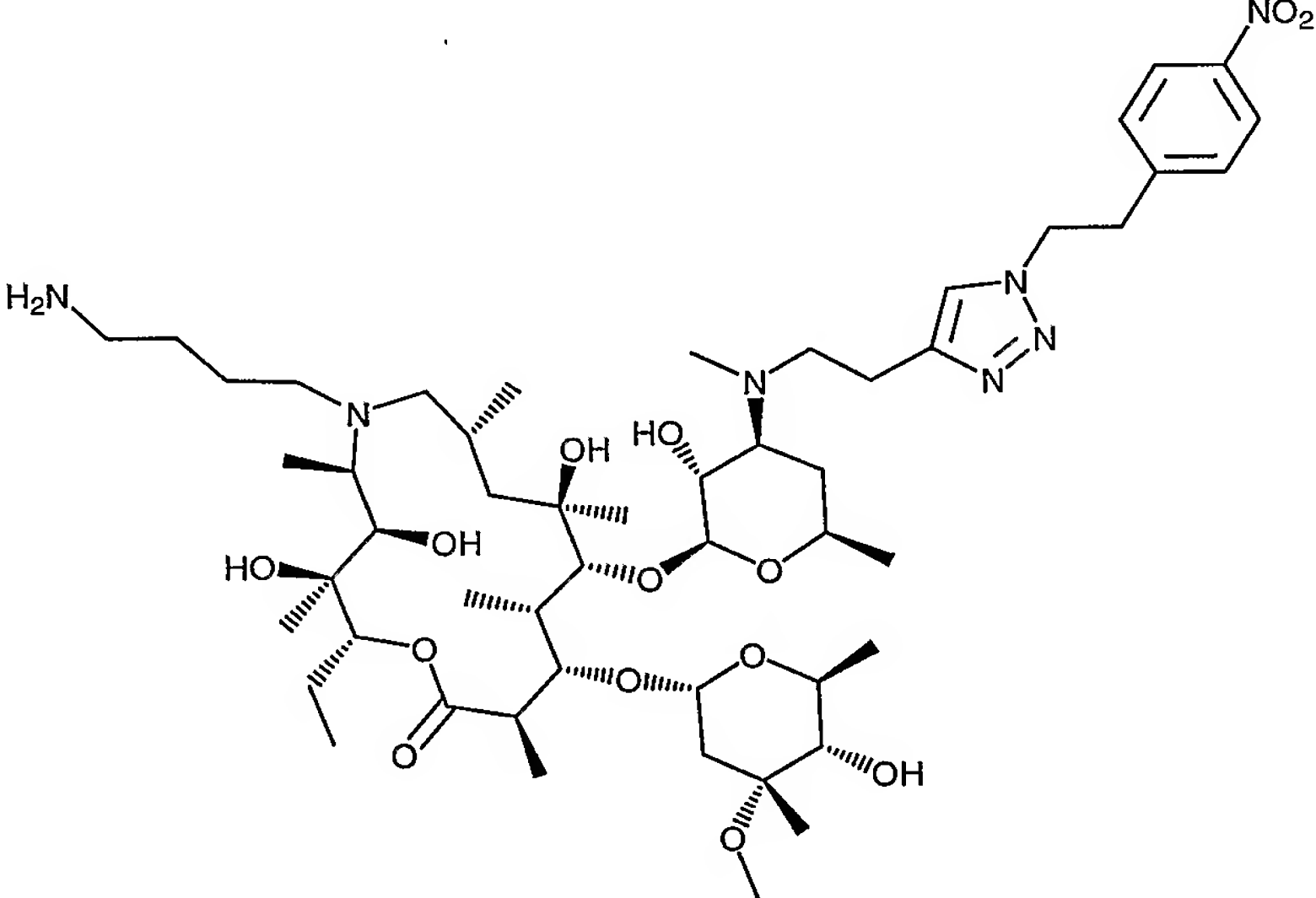
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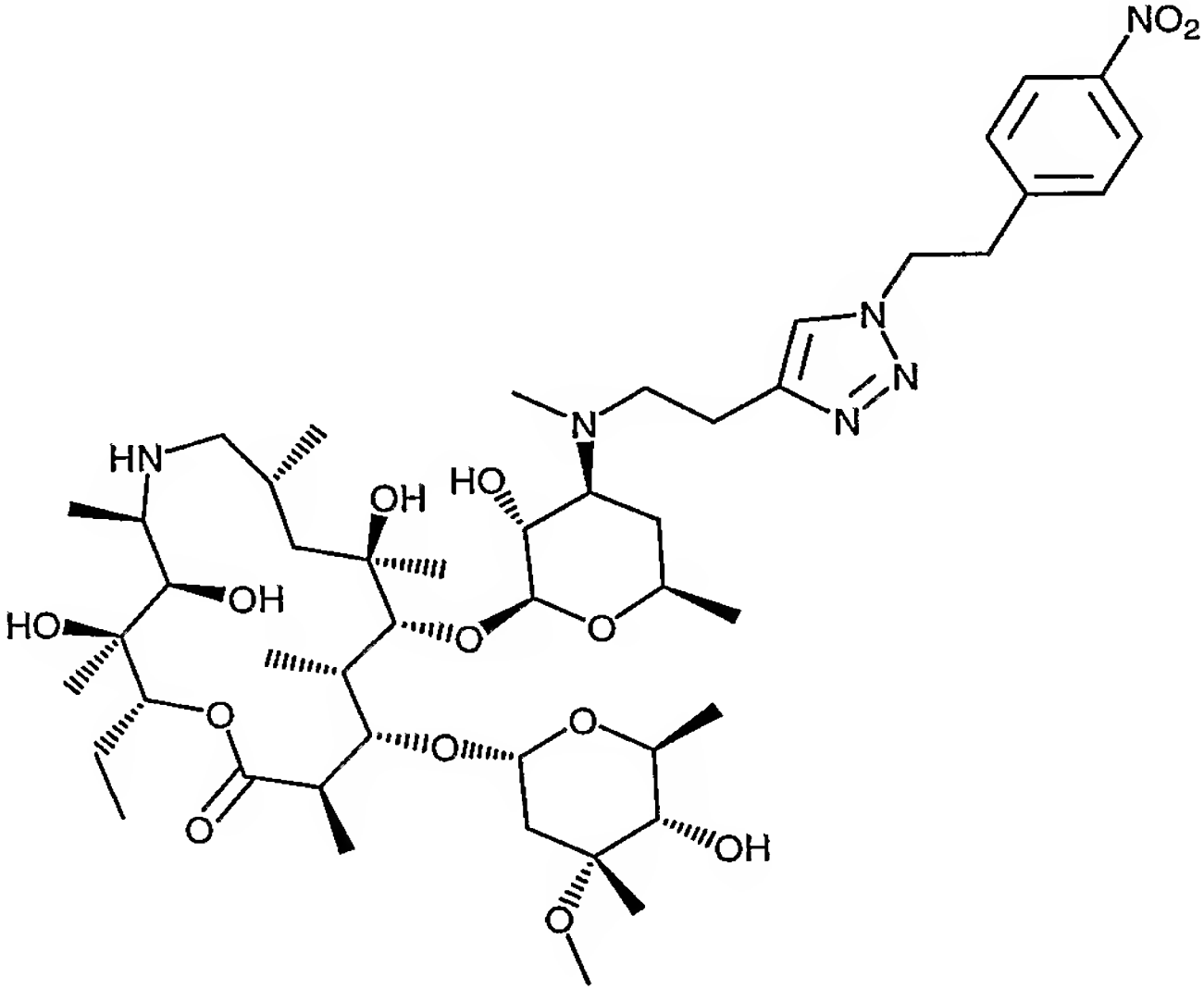
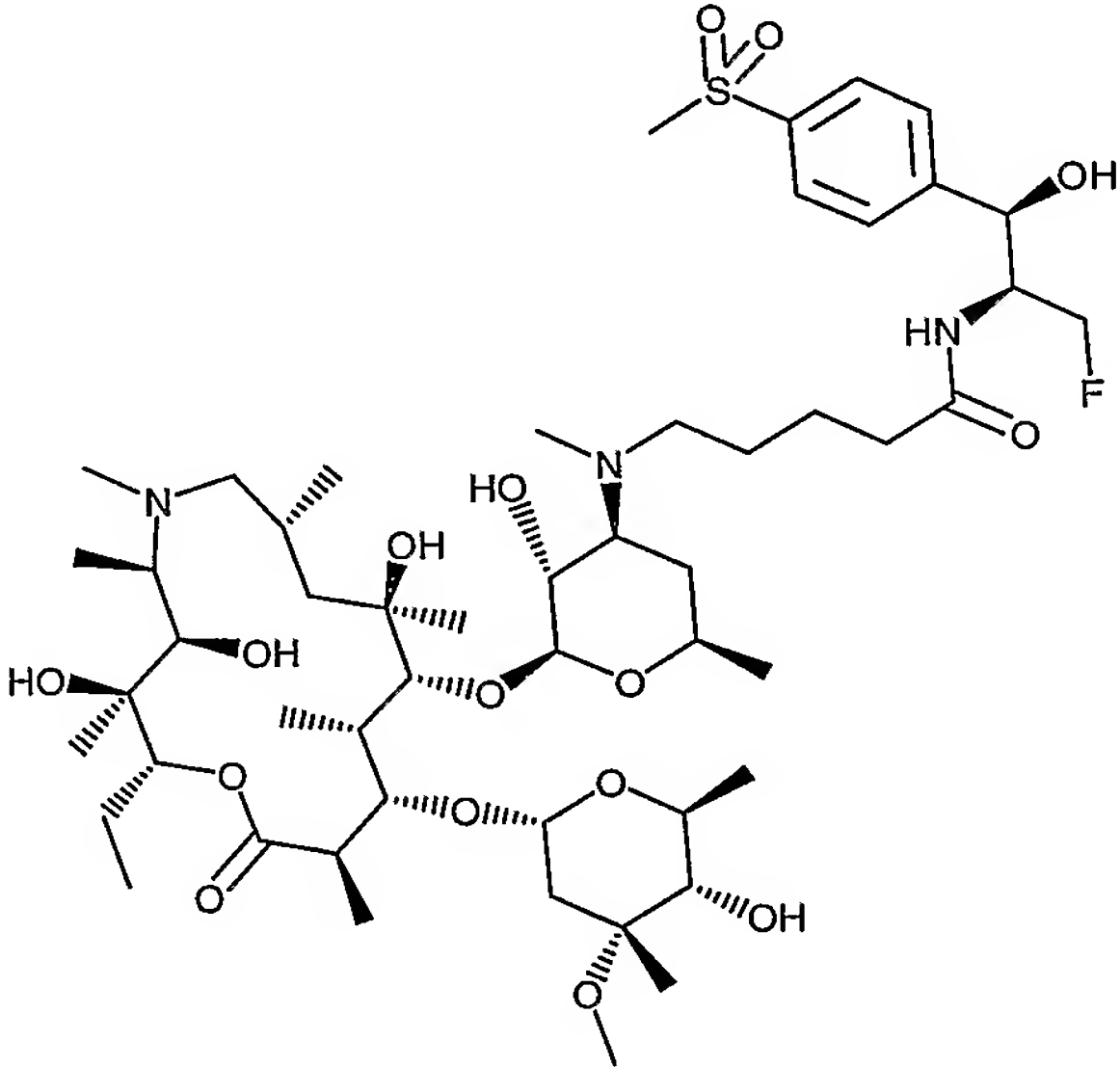
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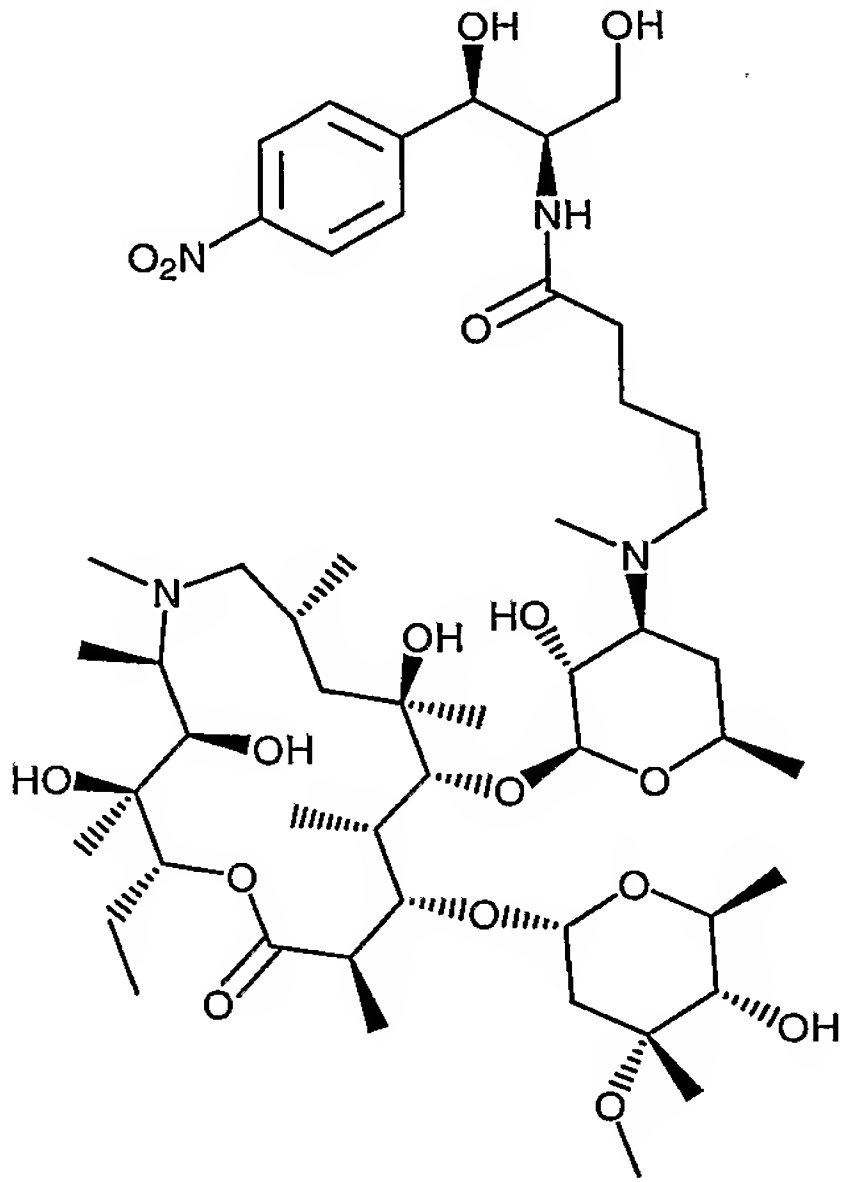
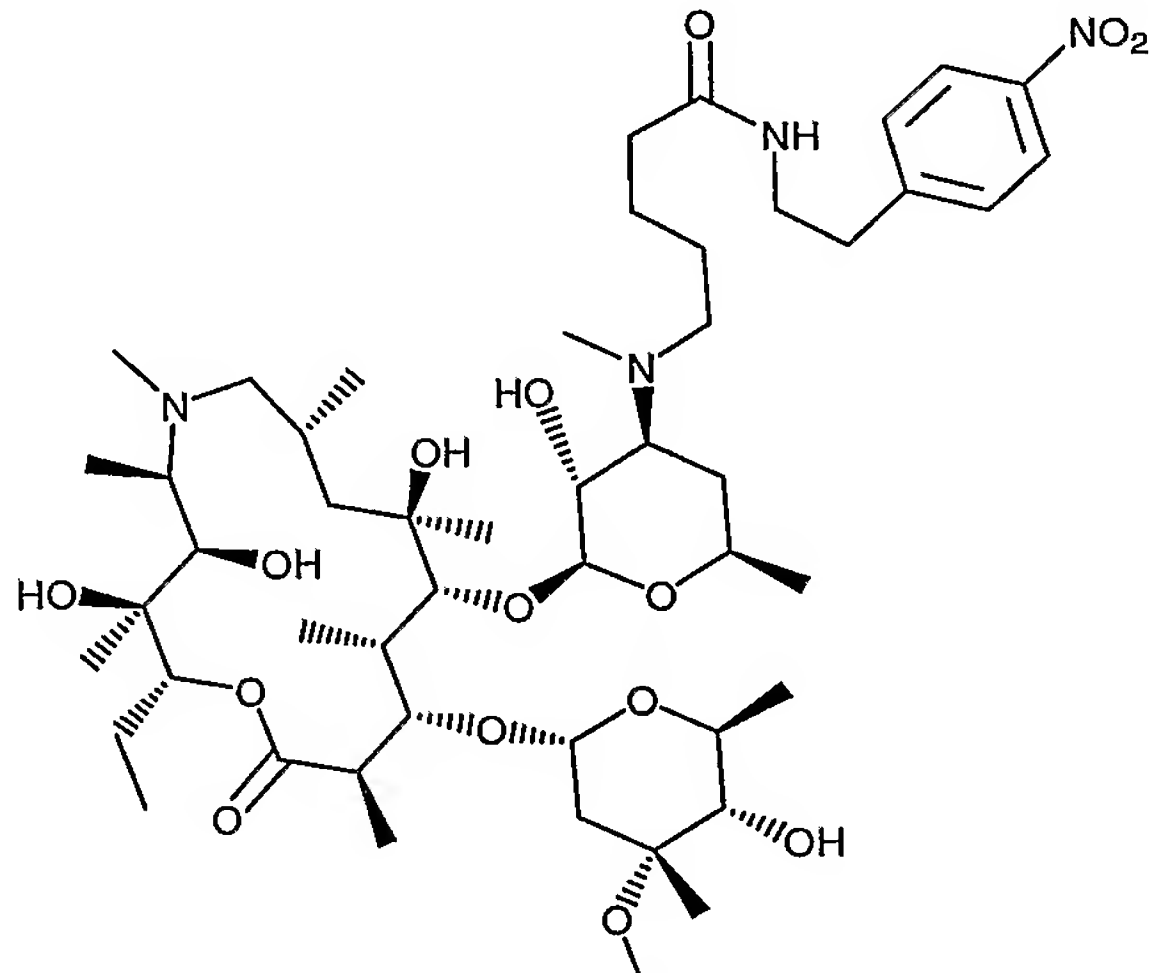
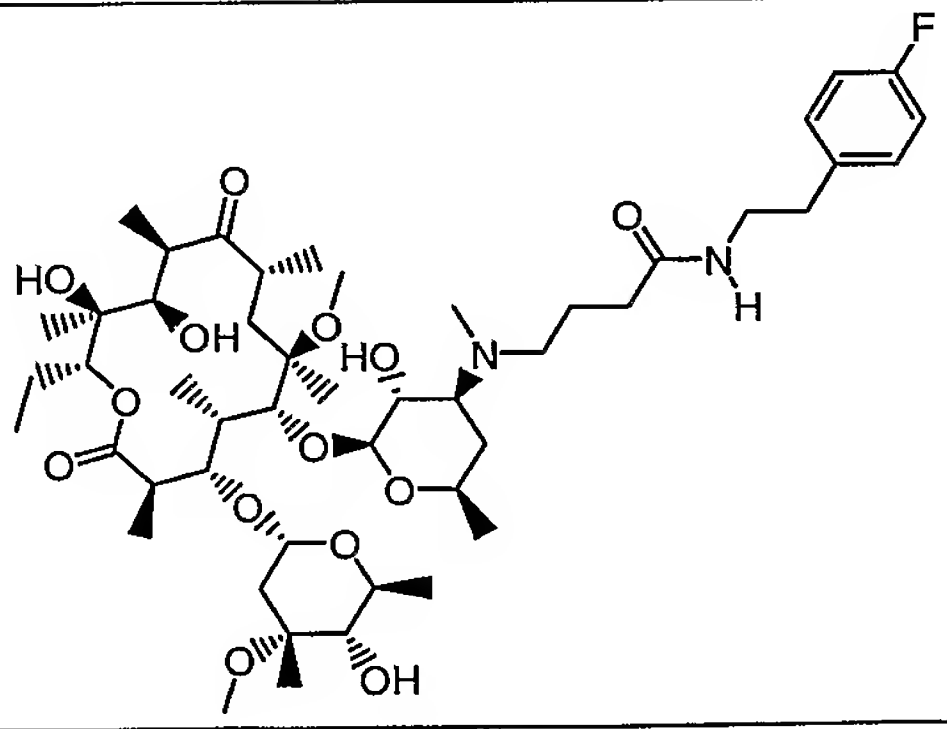
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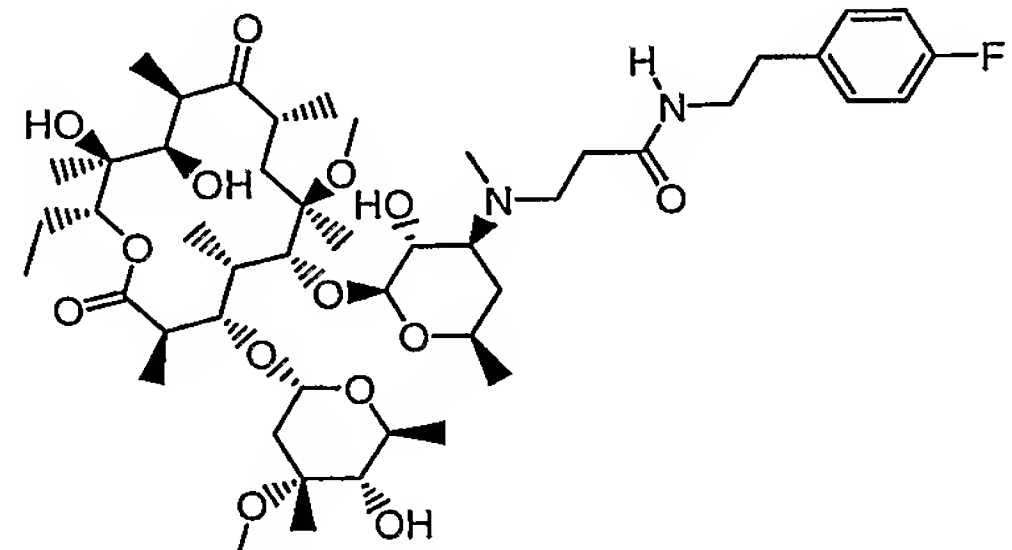
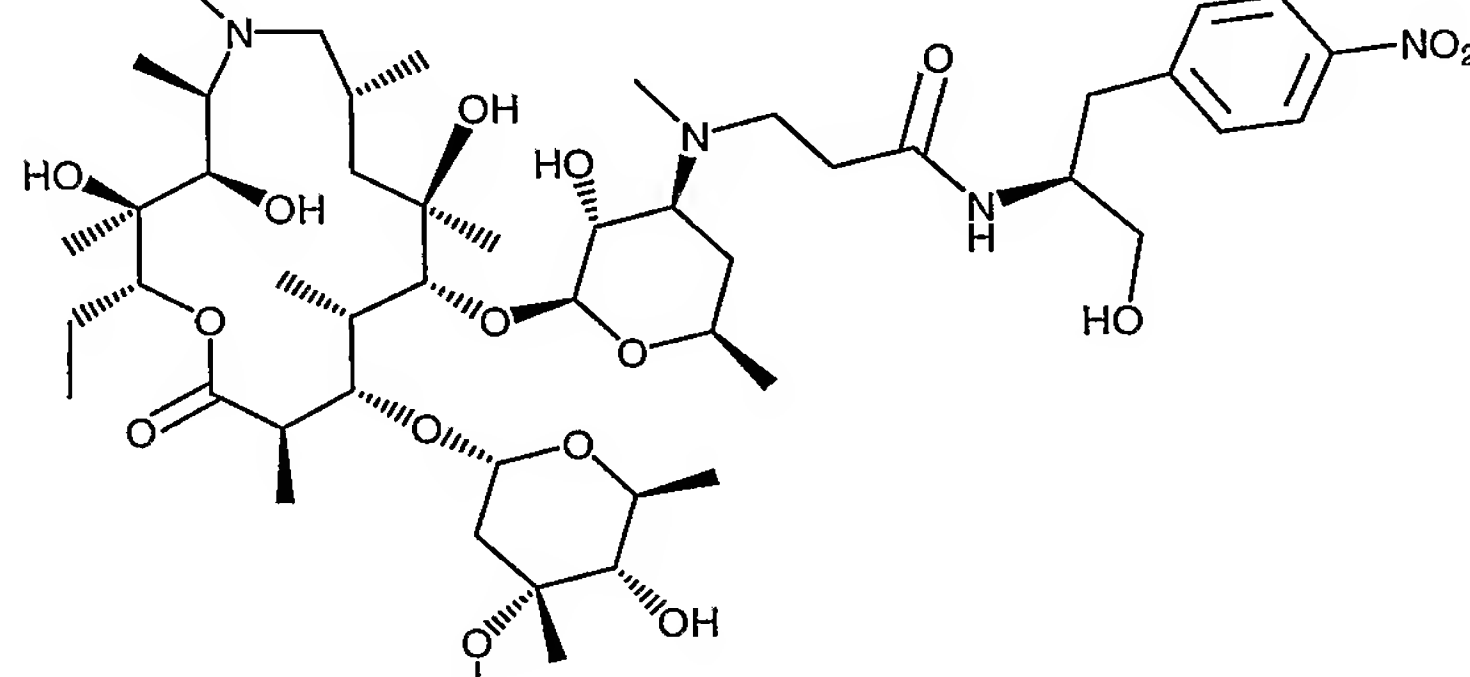
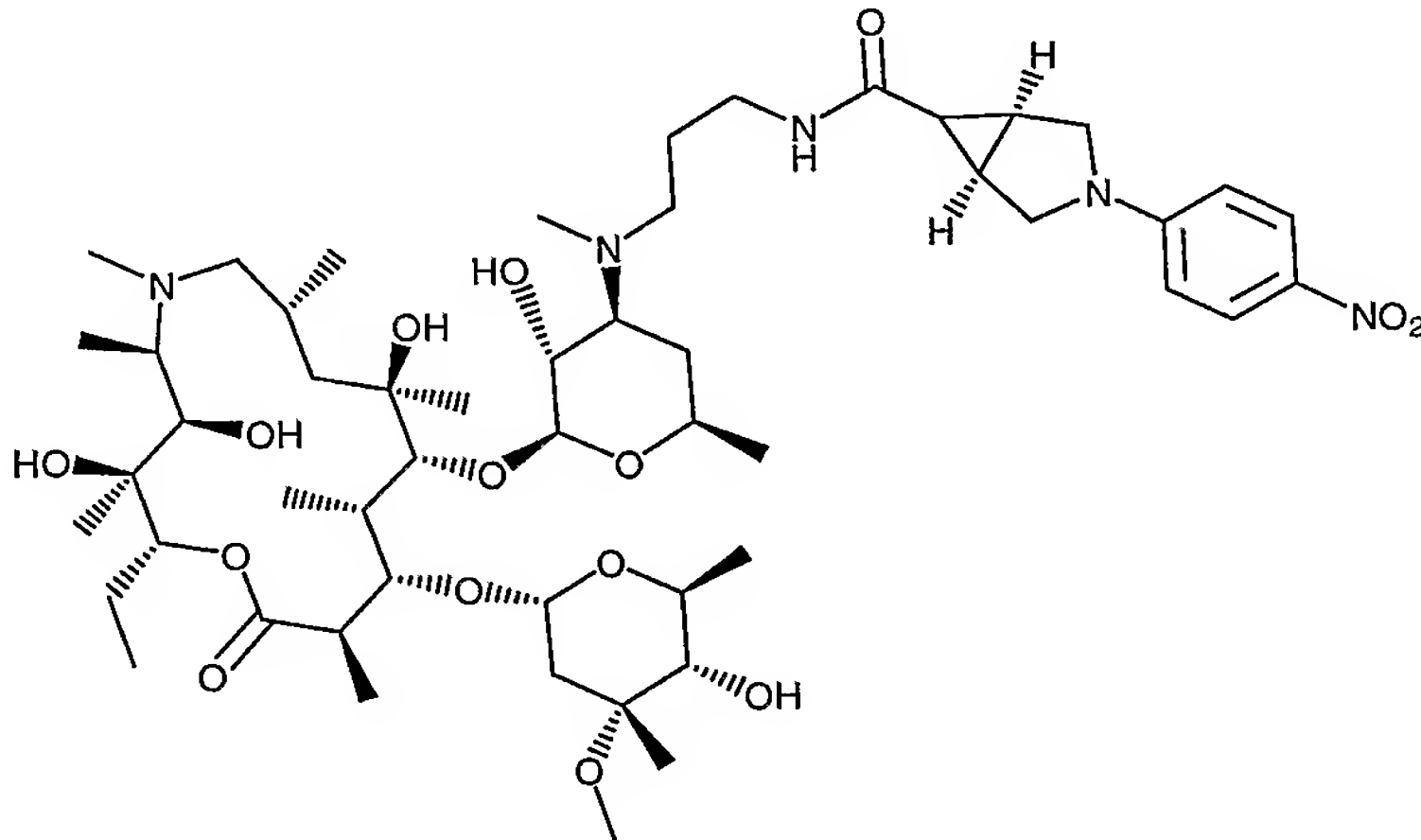
- 159 -

466	 <p>Chemical structure of compound 466, a complex molecule featuring a central core with multiple hydroxyl groups and a side chain containing a triazole ring and a 4-nitrophenyl group.</p>
475	 <p>Chemical structure of compound 475, a complex molecule featuring a central core with multiple hydroxyl groups and a side chain containing a sulfonamide group and a 4-fluorophenyl group.</p>

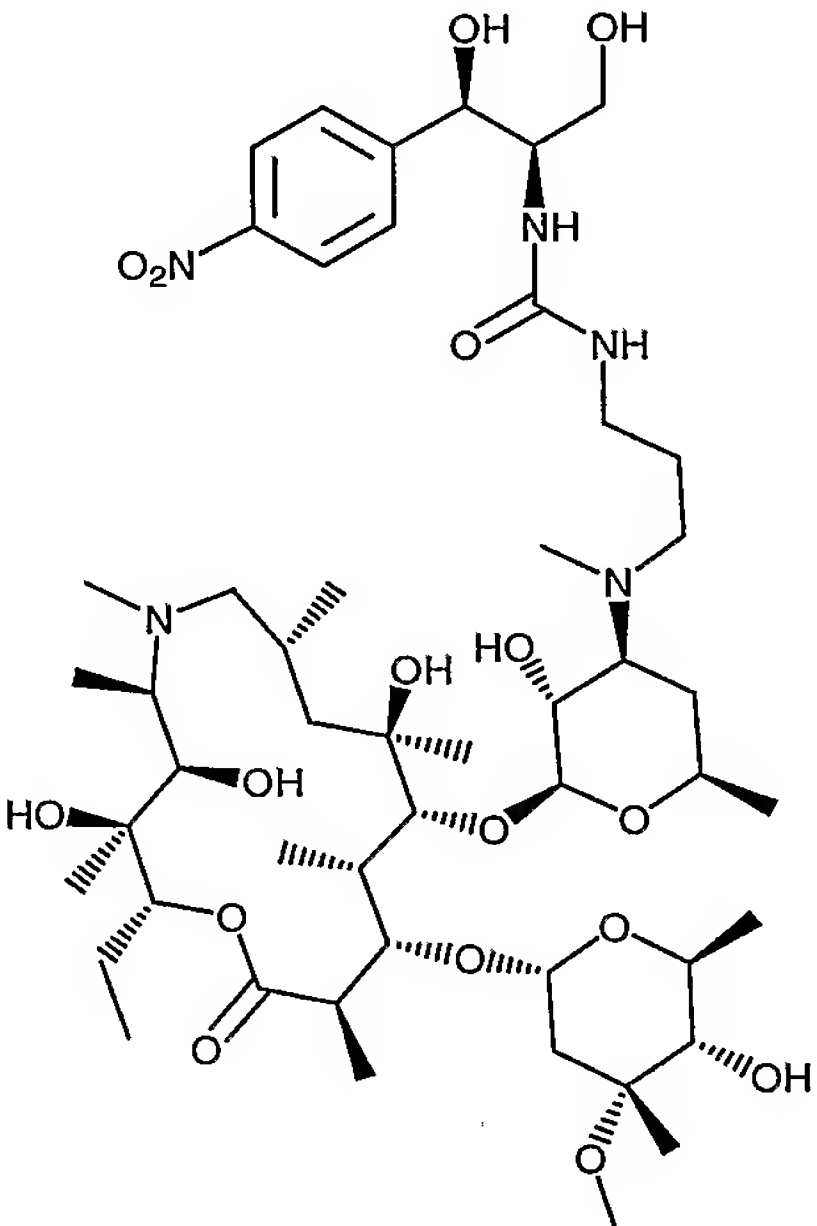
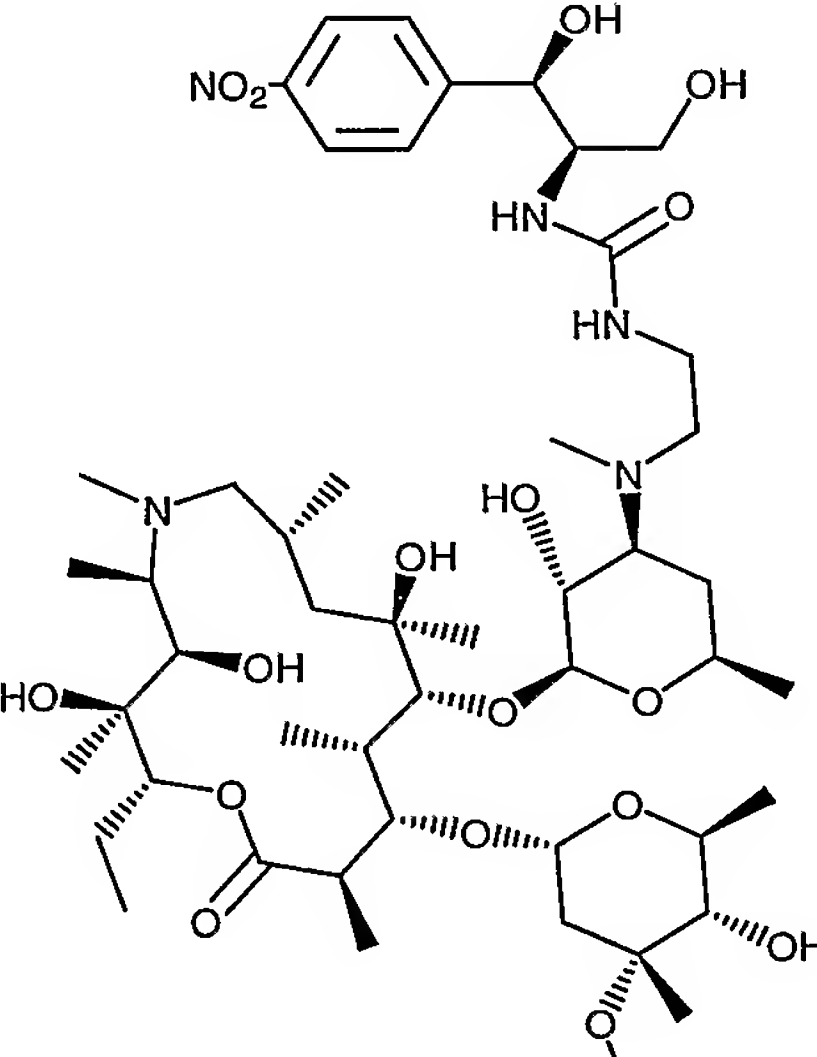
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476	 <p>Chemical structure 476 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a nitrophenyl side chain. The side chain includes a nitro group (O₂N) and a hydroxyl group (OH) on a benzene ring, connected to a chiral center with a hydroxyl group (OH) and a hydroxymethyl group (CH₂OH). This is further connected to a carbonyl group (C=O) and a long alkyl chain.</p>
477	 <p>Chemical structure 477 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a nitrophenyl side chain. The side chain includes a nitro group (NO₂) and a hydroxyl group (OH) on a benzene ring, connected to a chiral center with a hydroxyl group (OH) and a hydroxymethyl group (CH₂OH). This is further connected to a carbonyl group (C=O) and a long alkyl chain.</p>
478	 <p>Chemical structure 478 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups and a fluorophenyl side chain. The side chain includes a fluorine atom (F) on a benzene ring, connected to a chiral center with a hydroxyl group (OH) and a hydroxymethyl group (CH₂OH). This is further connected to a carbonyl group (C=O) and a long alkyl chain.</p>

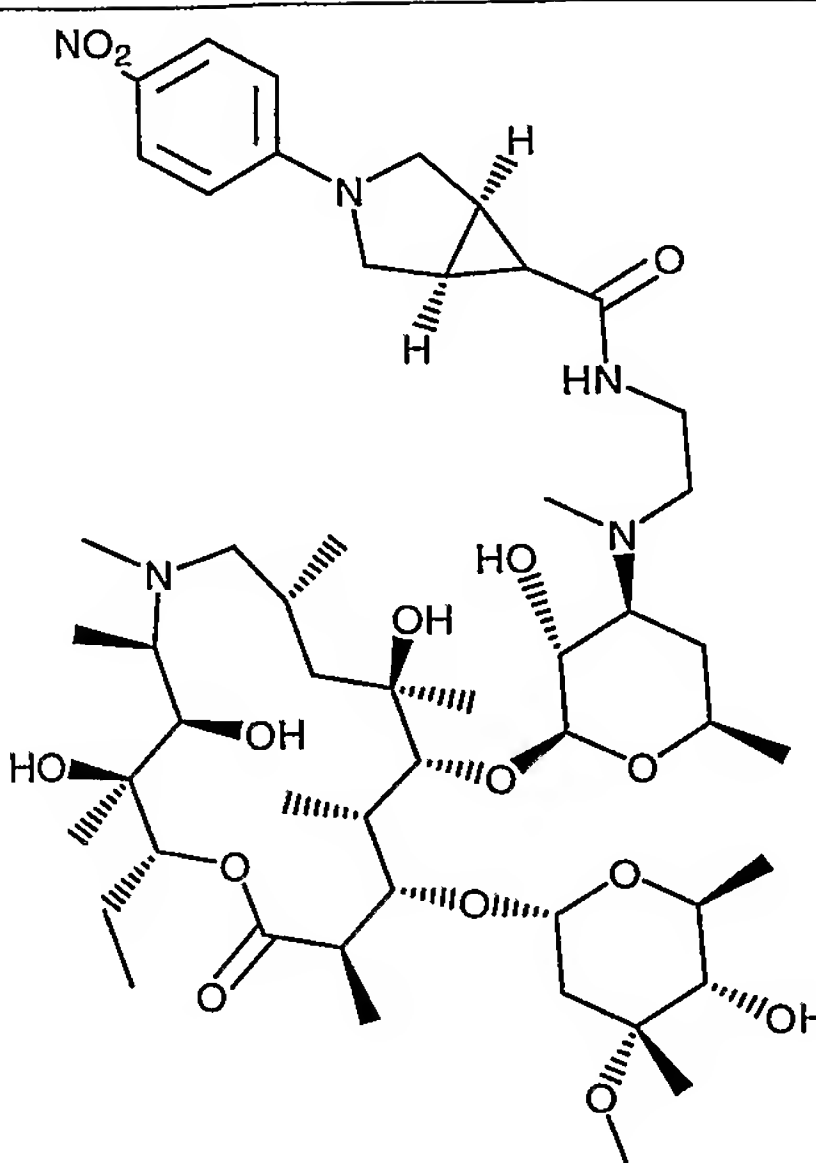
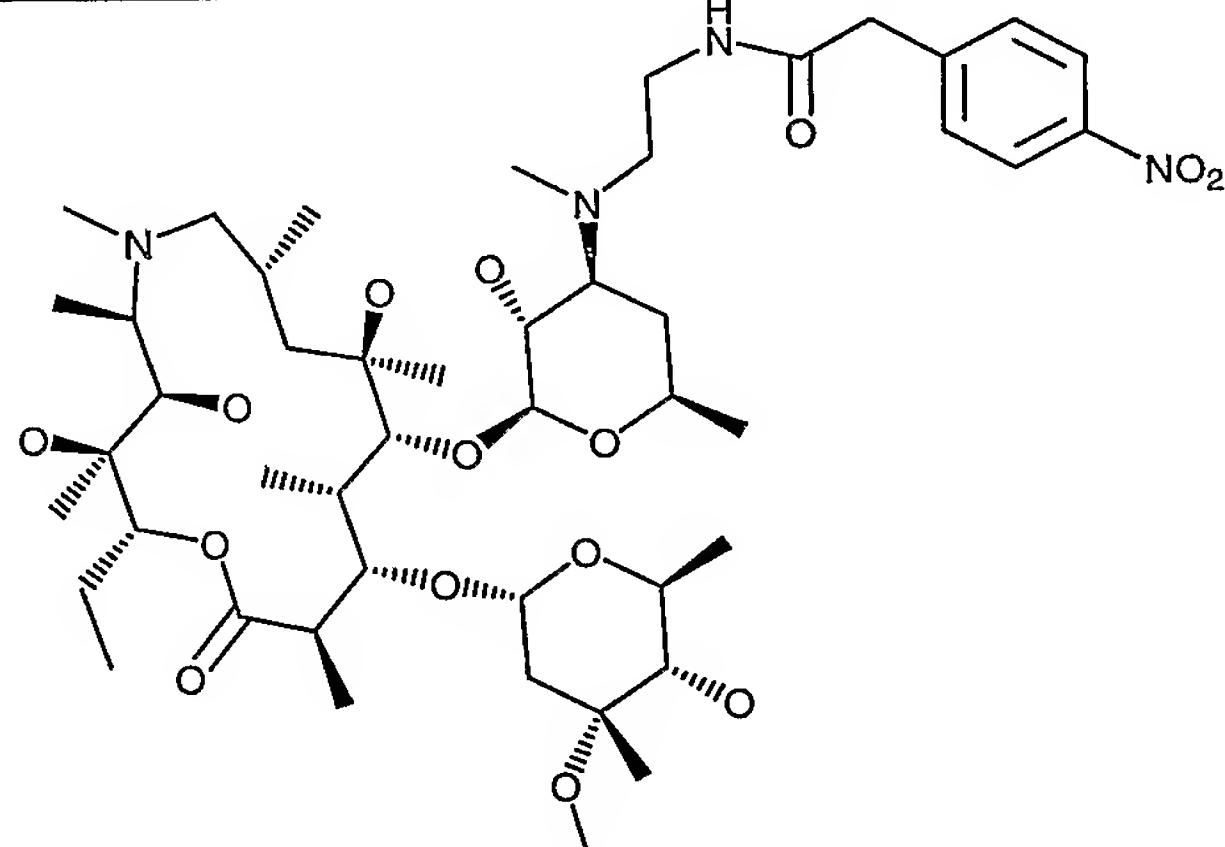
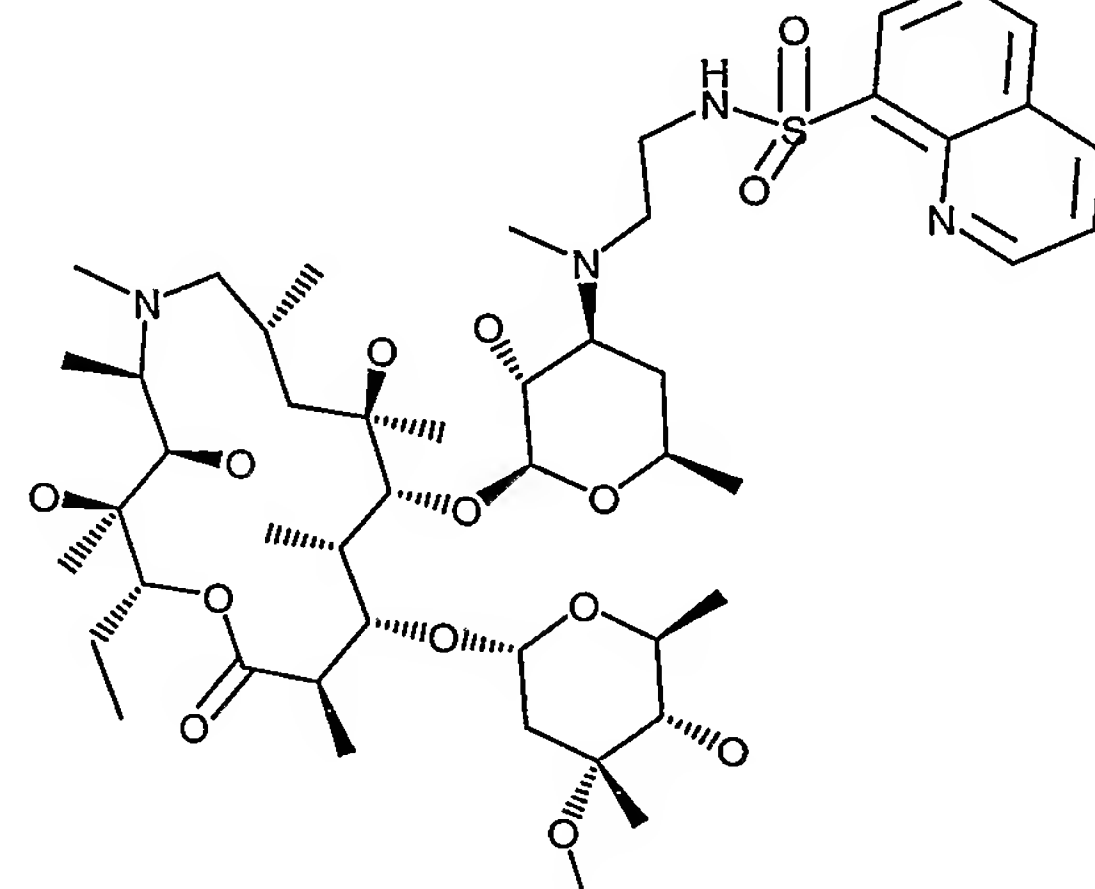
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479	 <p>Chemical structure 479: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a p-fluorophenyl group.</p>
480	 <p>Chemical structure 480: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a p-nitrophenyl group.</p>
501	 <p>Chemical structure 501: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a p-nitrophenyl group.</p>

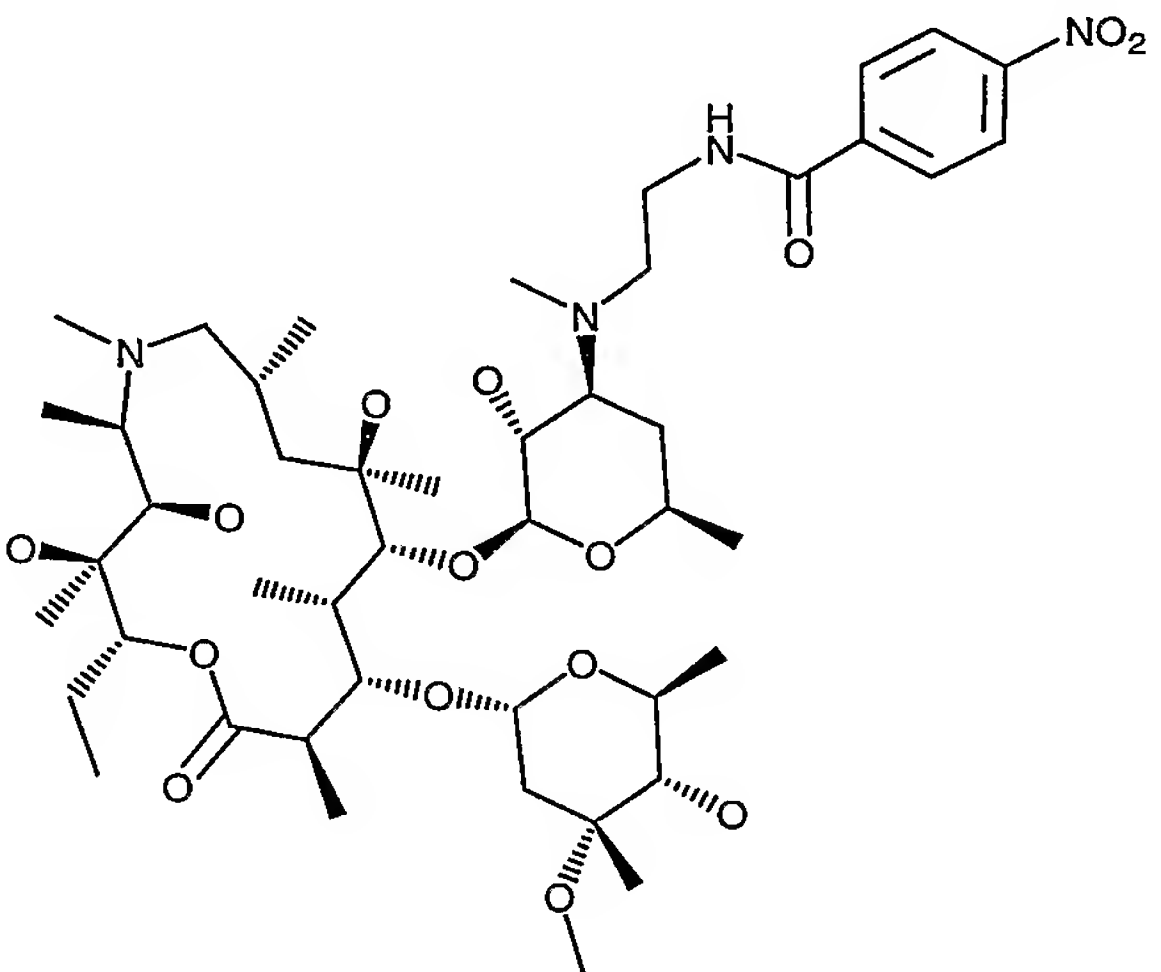
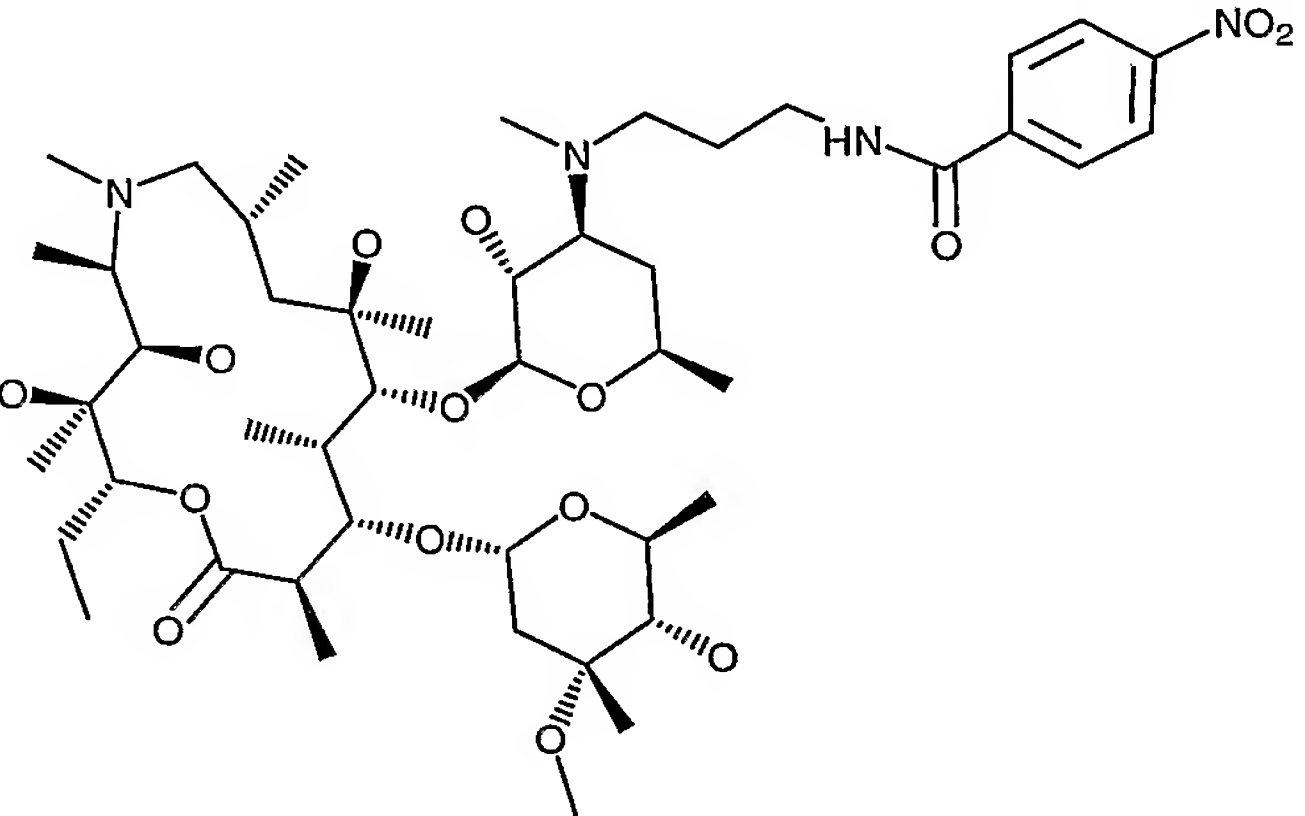
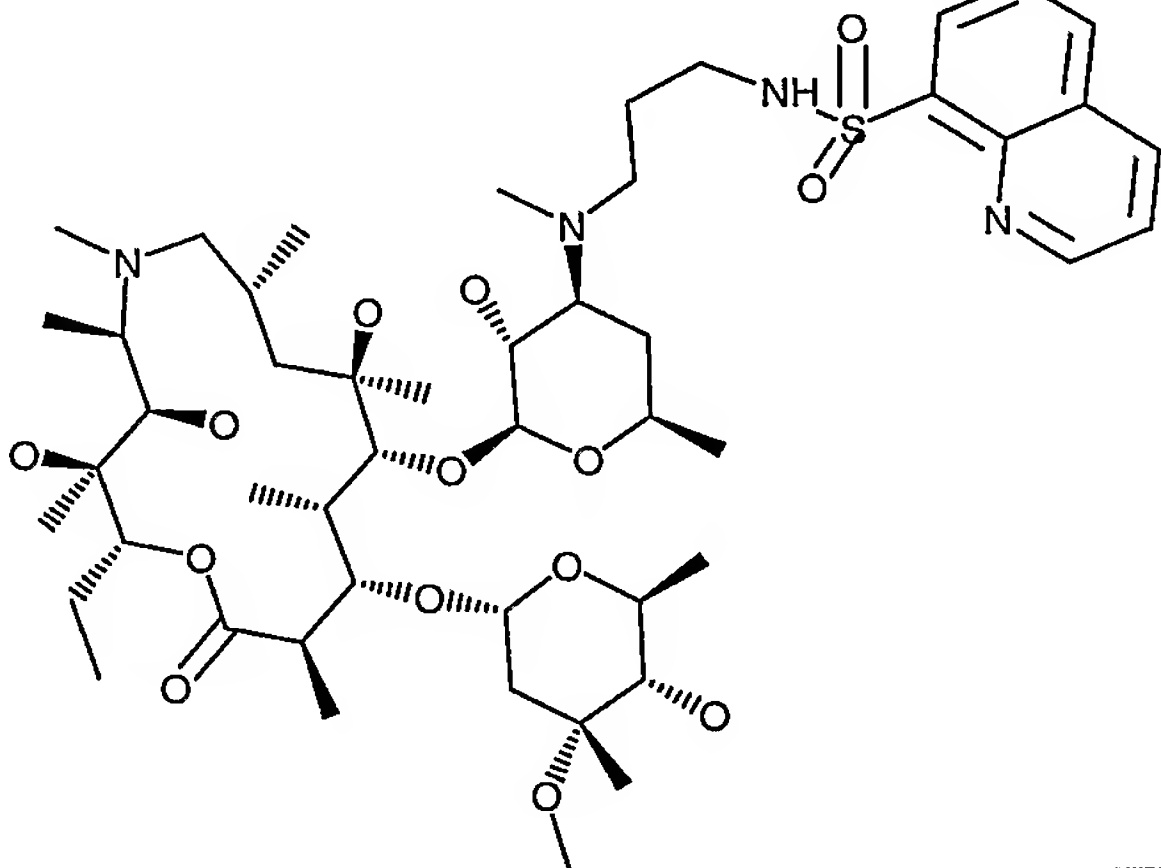
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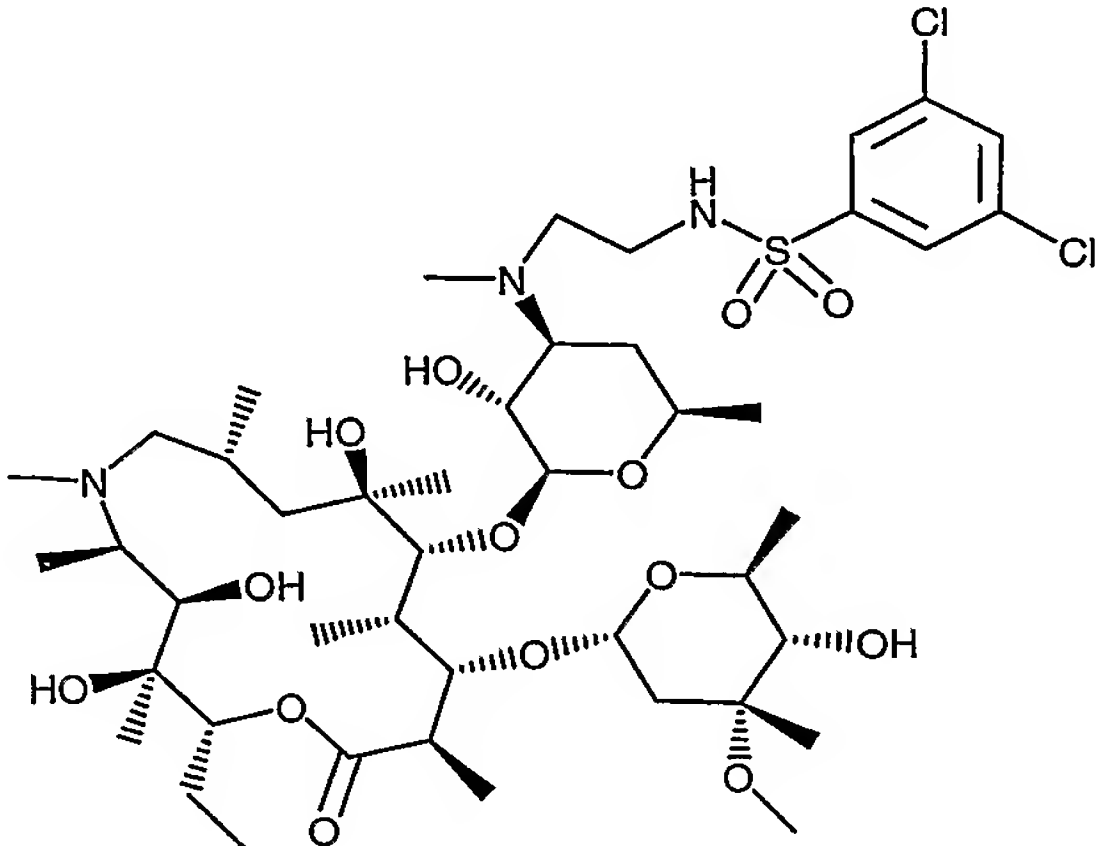
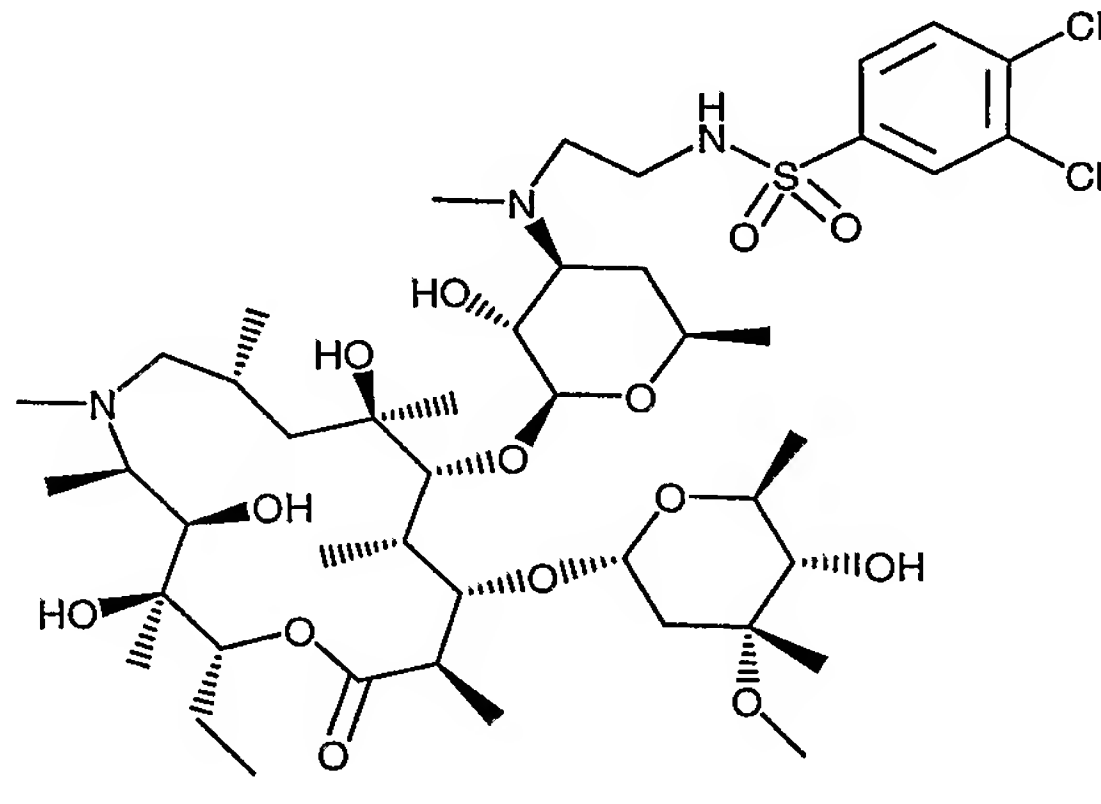
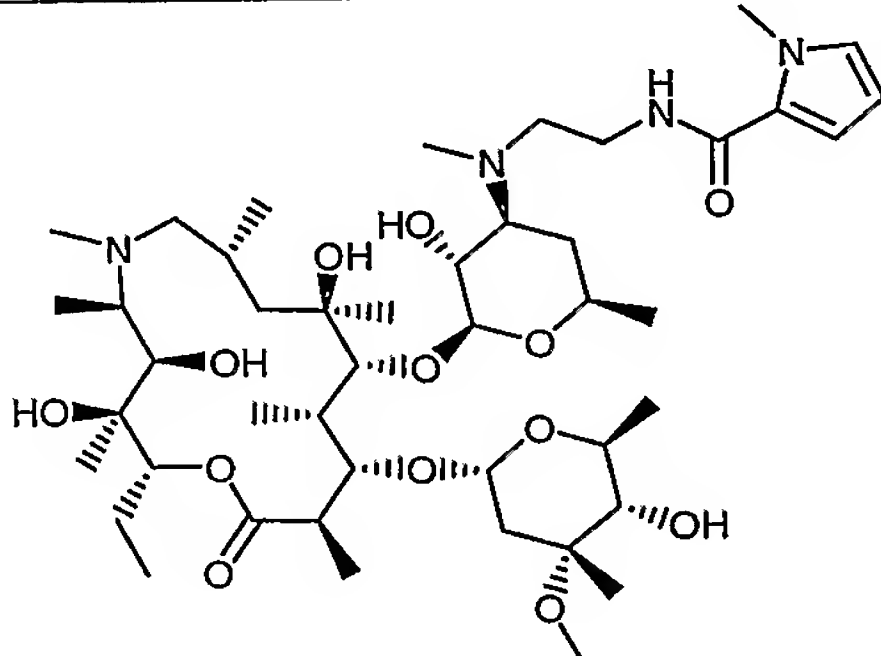
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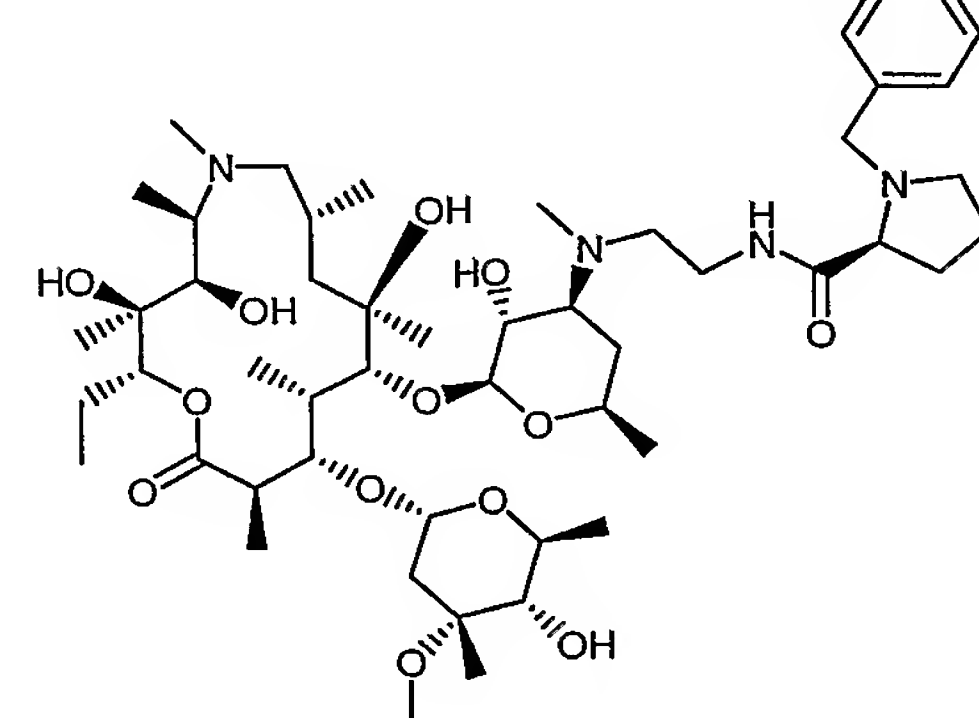
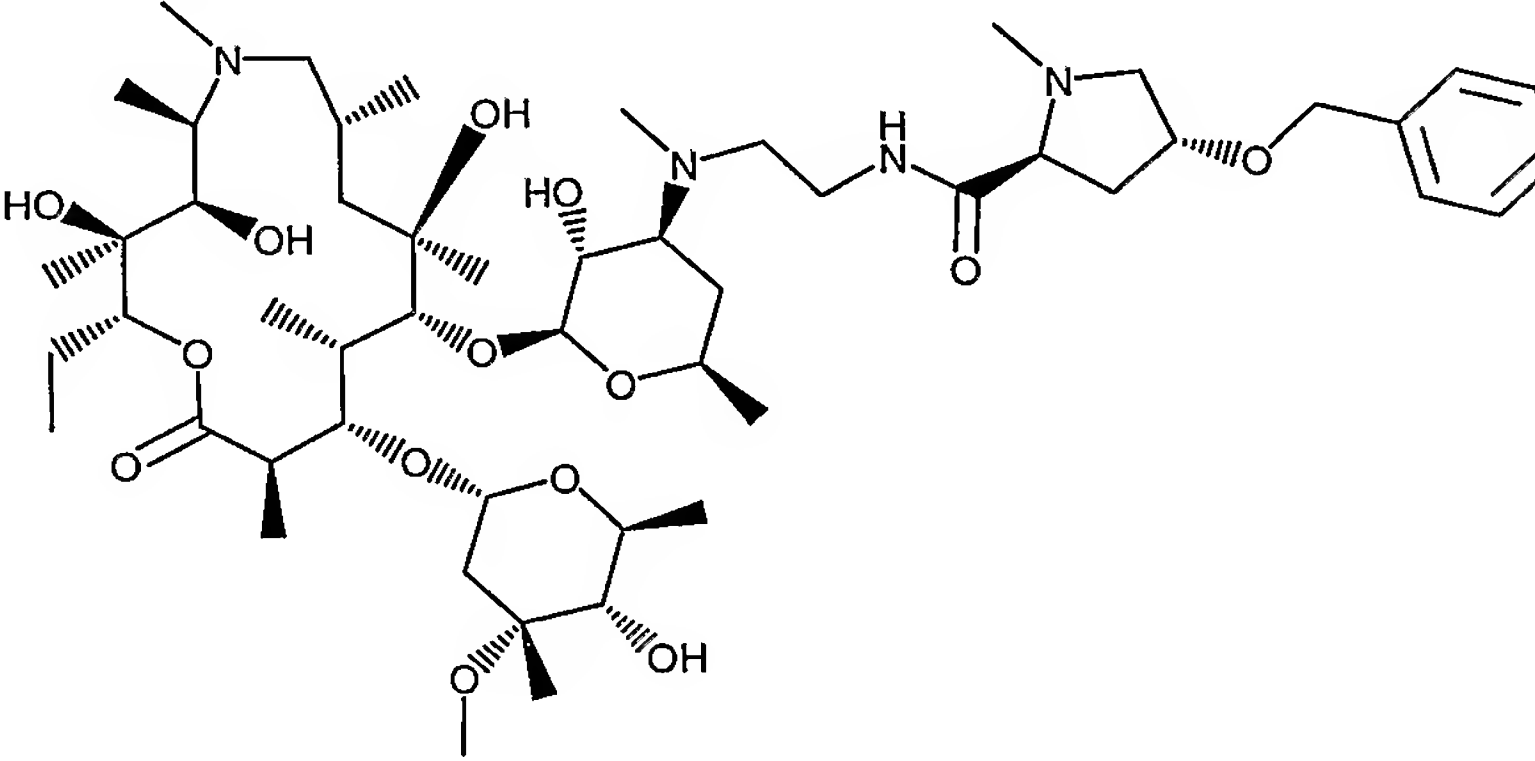
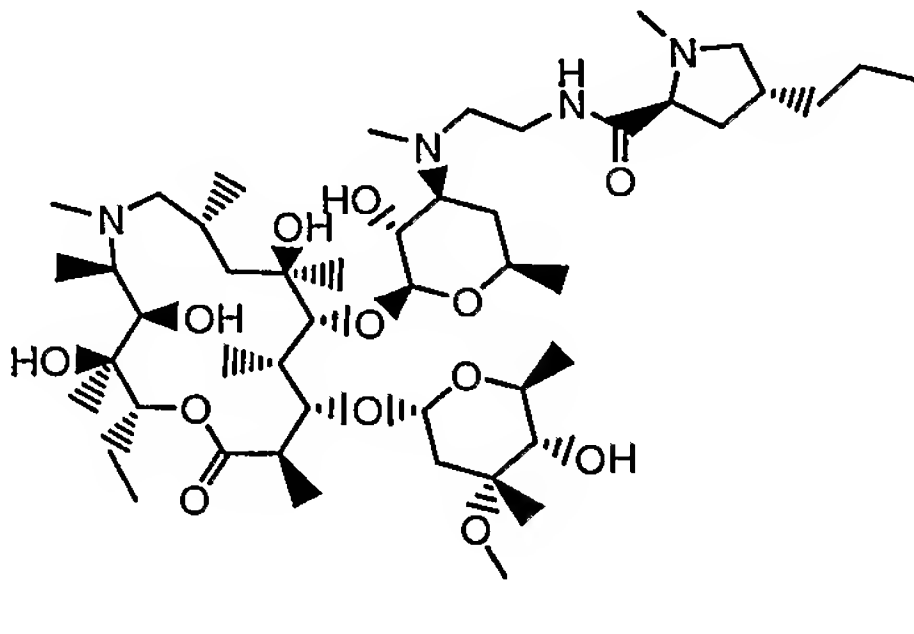
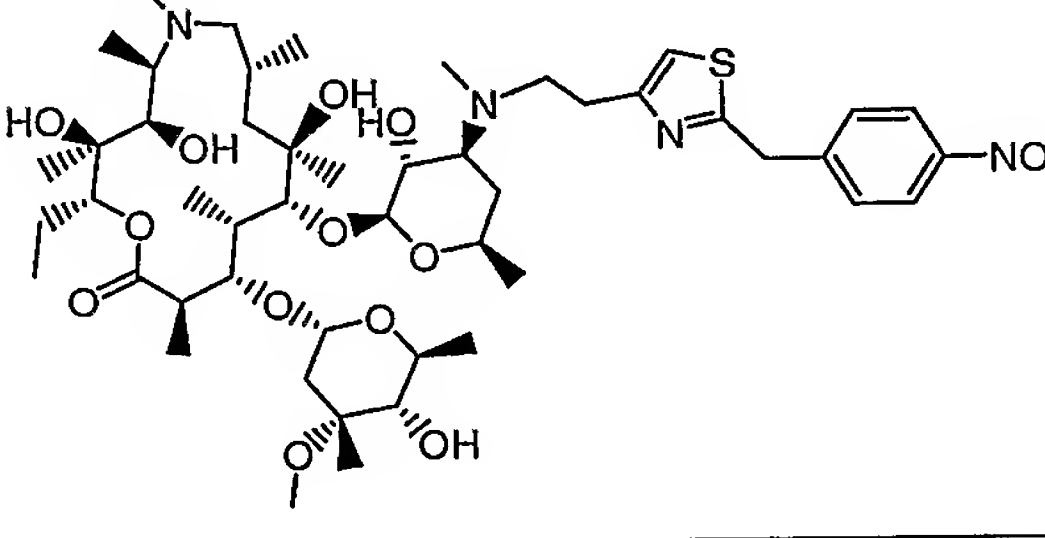
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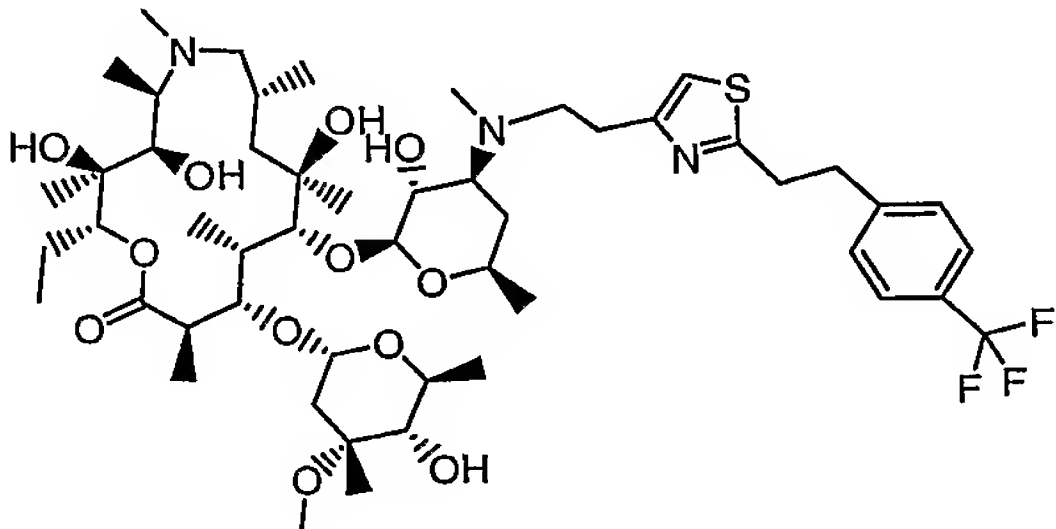
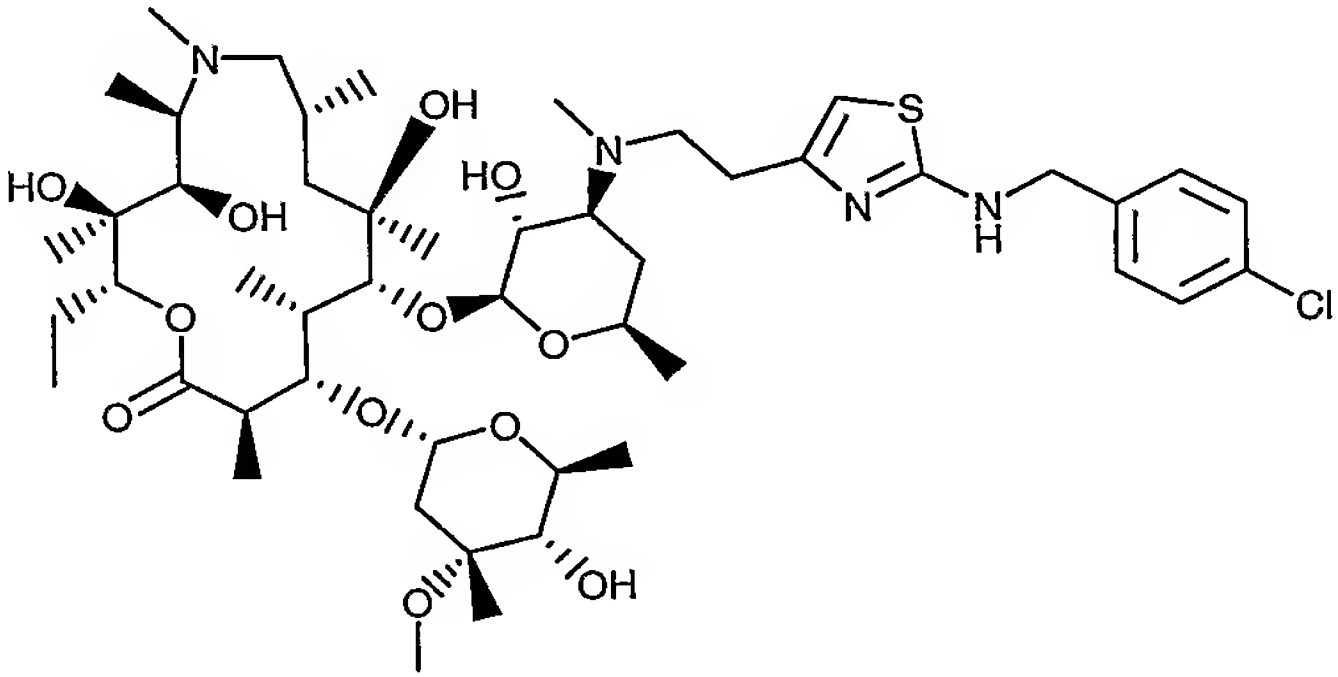
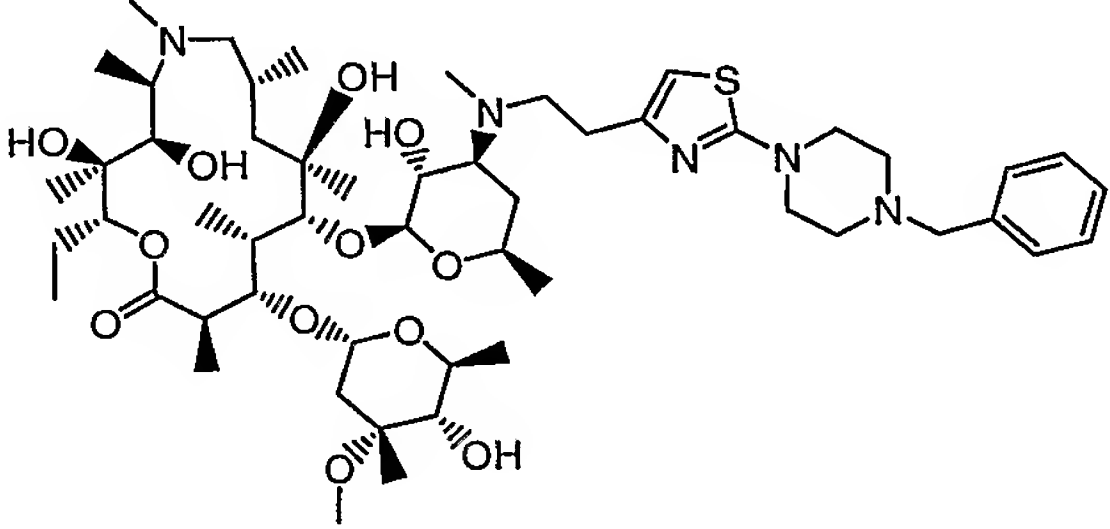
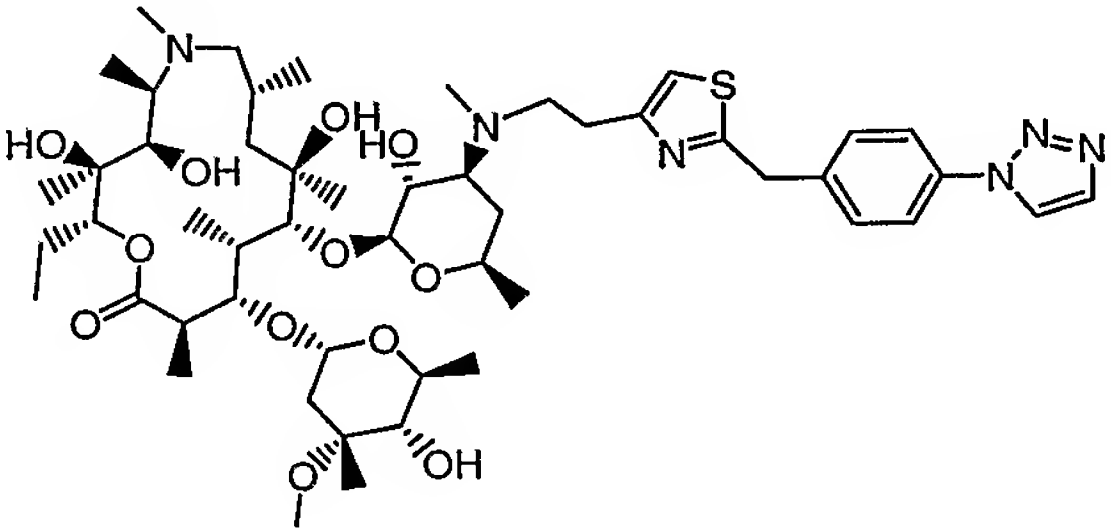
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510	 <p>Chemical structure 510 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a sulfonamide group linked to a 3,5-dichlorophenyl ring.</p>
511	 <p>Chemical structure 511 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a sulfonamide group linked to a 3,5-dichlorophenyl ring.</p>
512	 <p>Chemical structure 512 is a complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a sulfonamide group linked to a pyridine ring.</p>

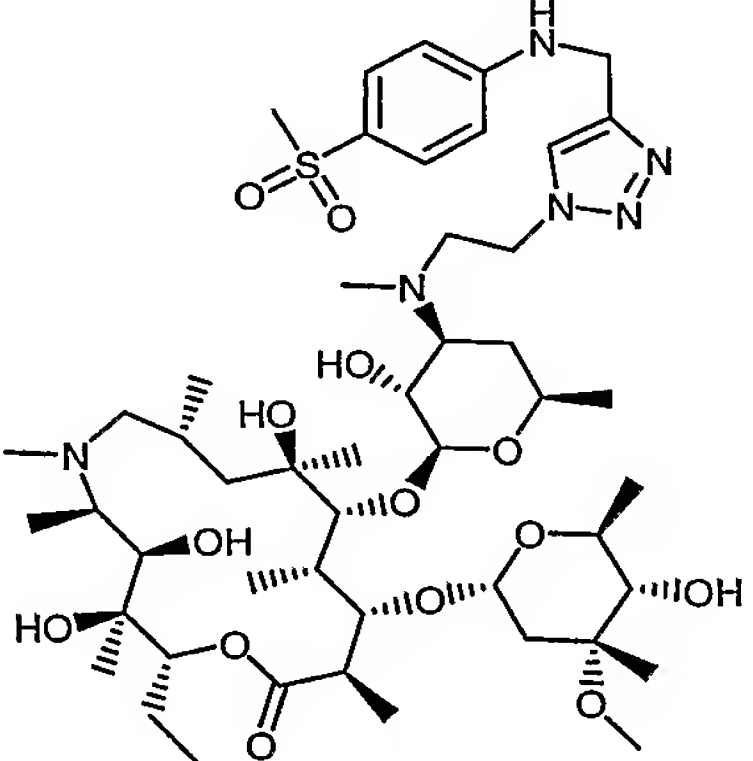
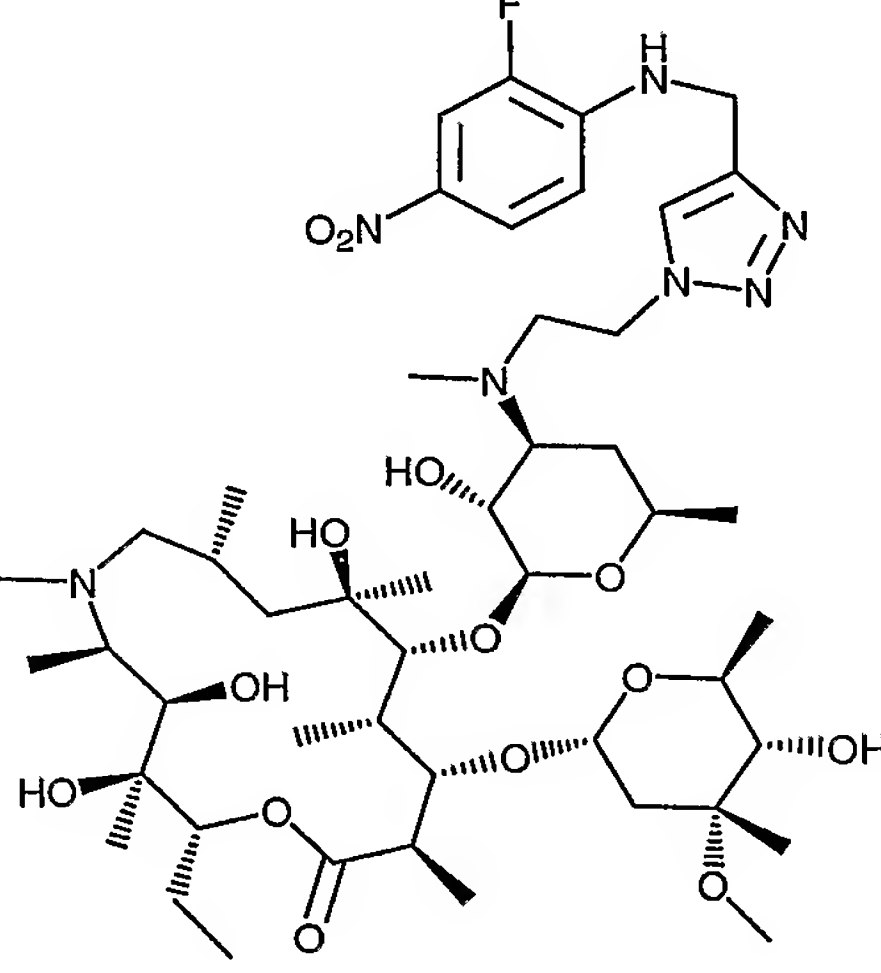
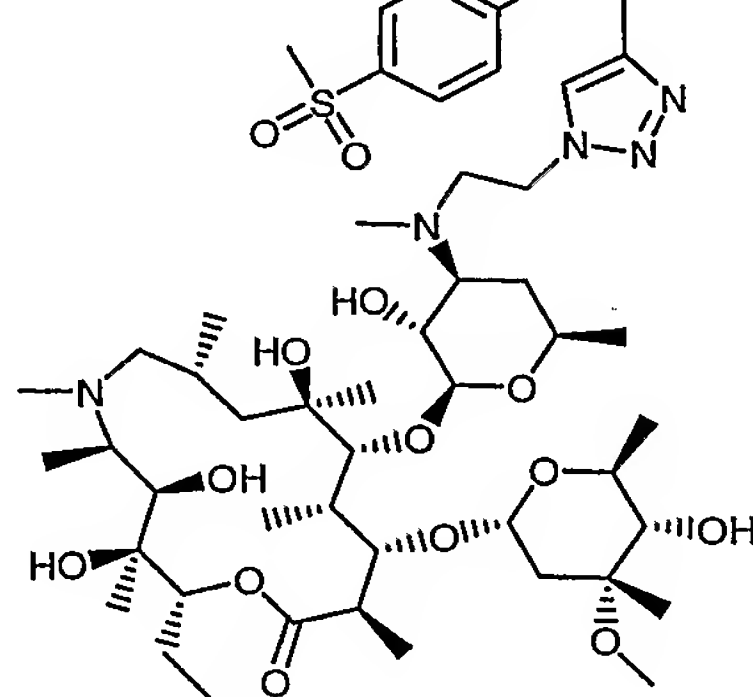
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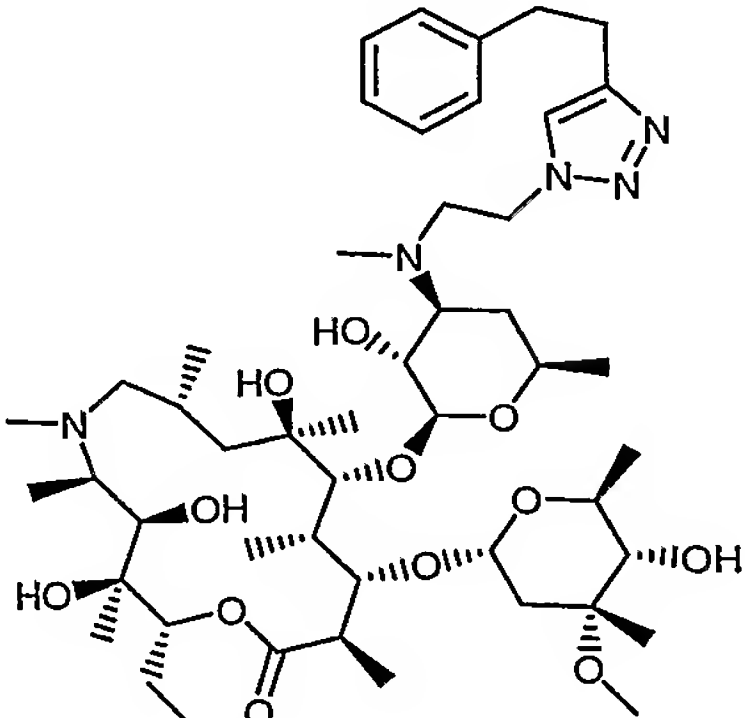
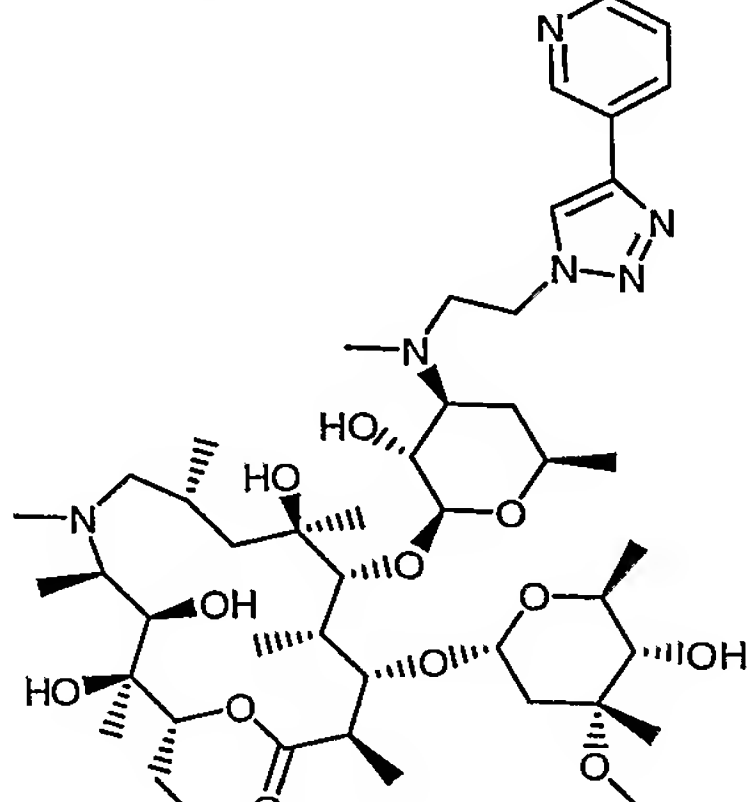
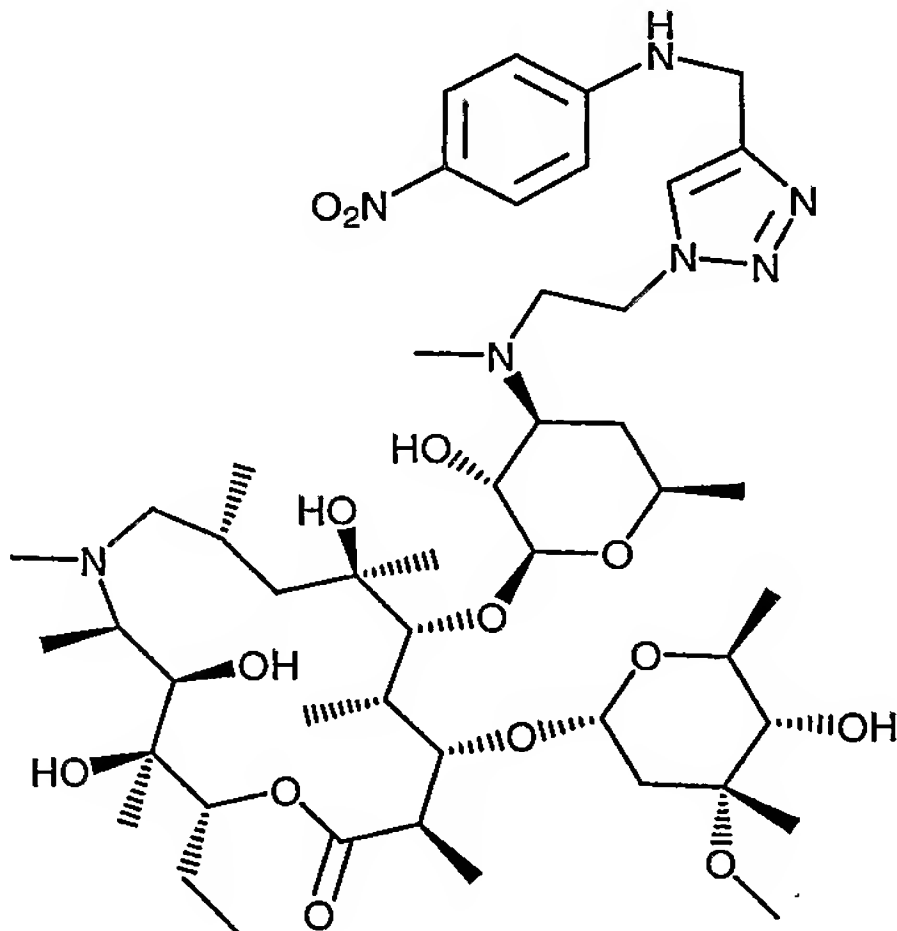
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526	 <p>Chemical structure 526: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a trifluoromethylphenyl group attached via a thiazole ring.</p>
527	 <p>Chemical structure 527: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a 4-chlorophenyl group attached via a thiazole ring.</p>
528	 <p>Chemical structure 528: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a benzyl group attached via a thiazole ring.</p>
529	 <p>Chemical structure 529: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a 1H-tetrazol-5-ylmethyl group attached via a thiazole ring.</p>

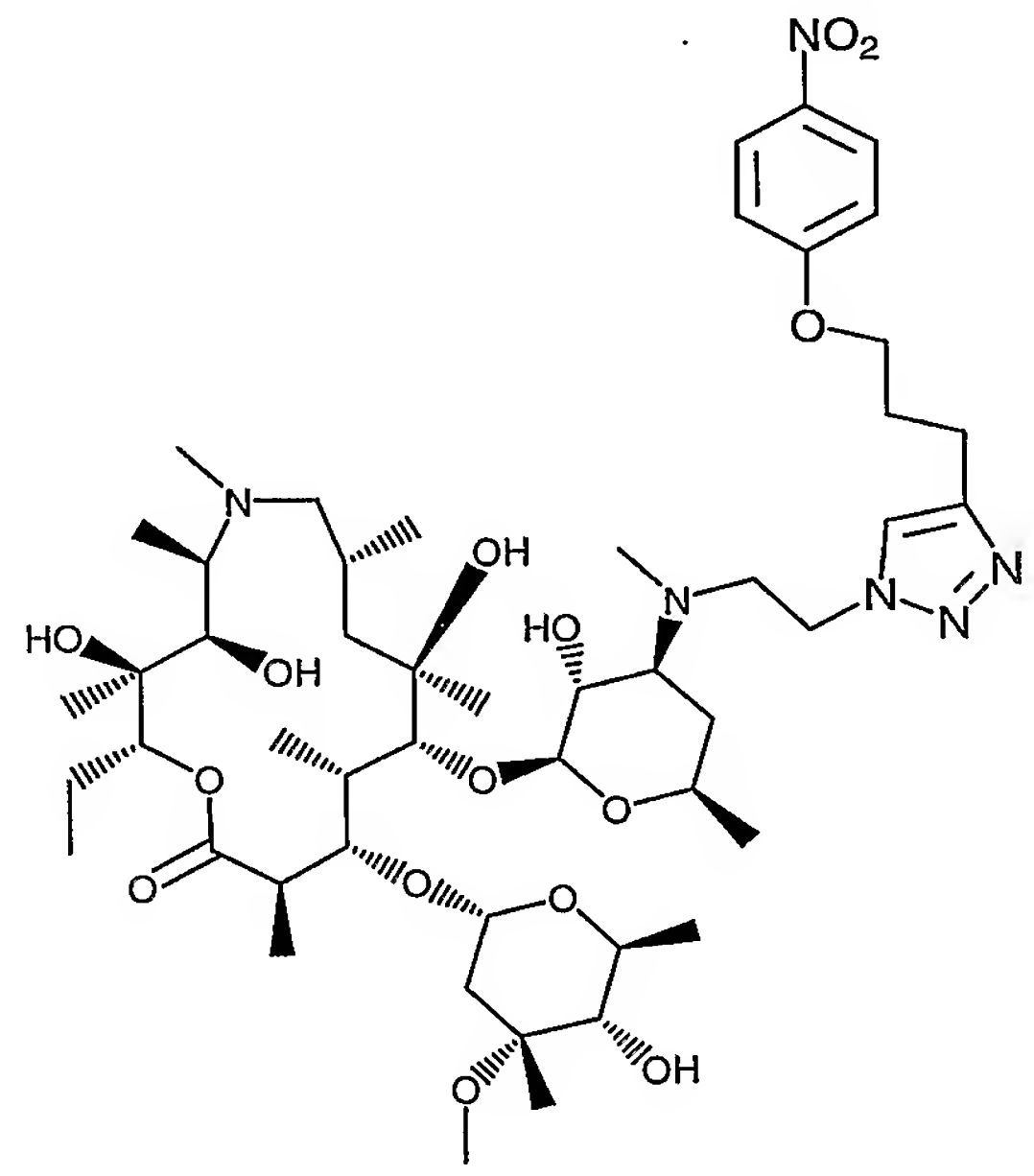
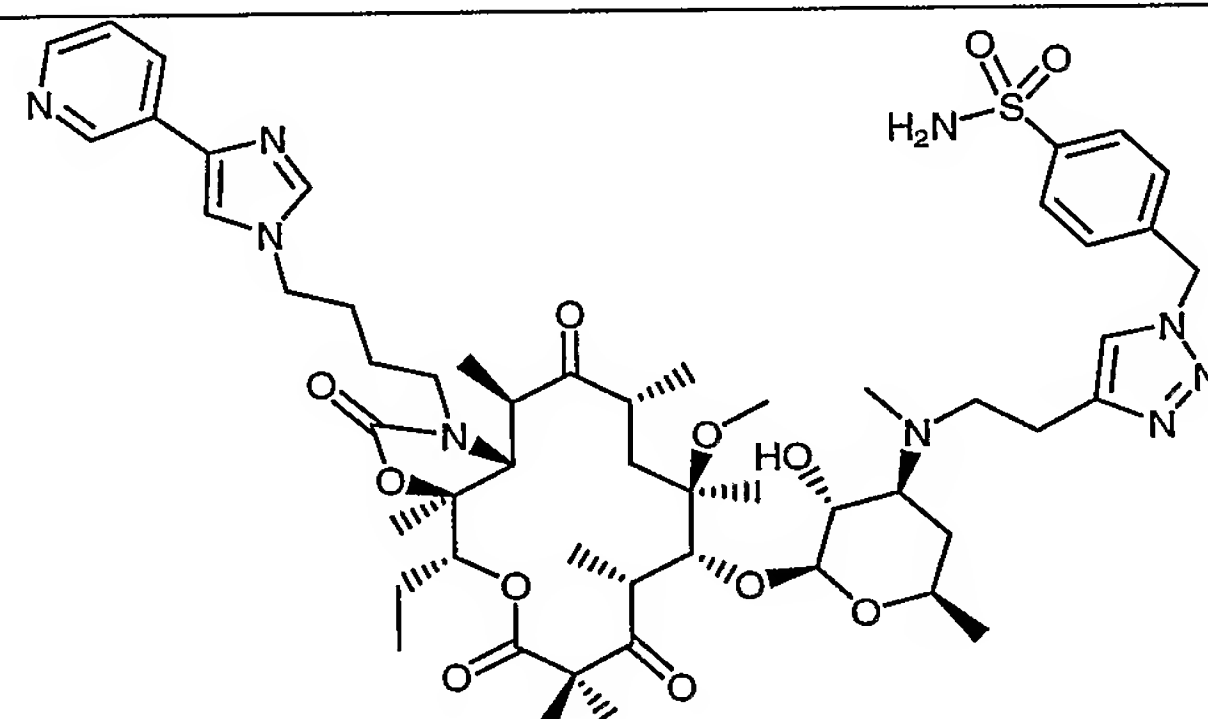
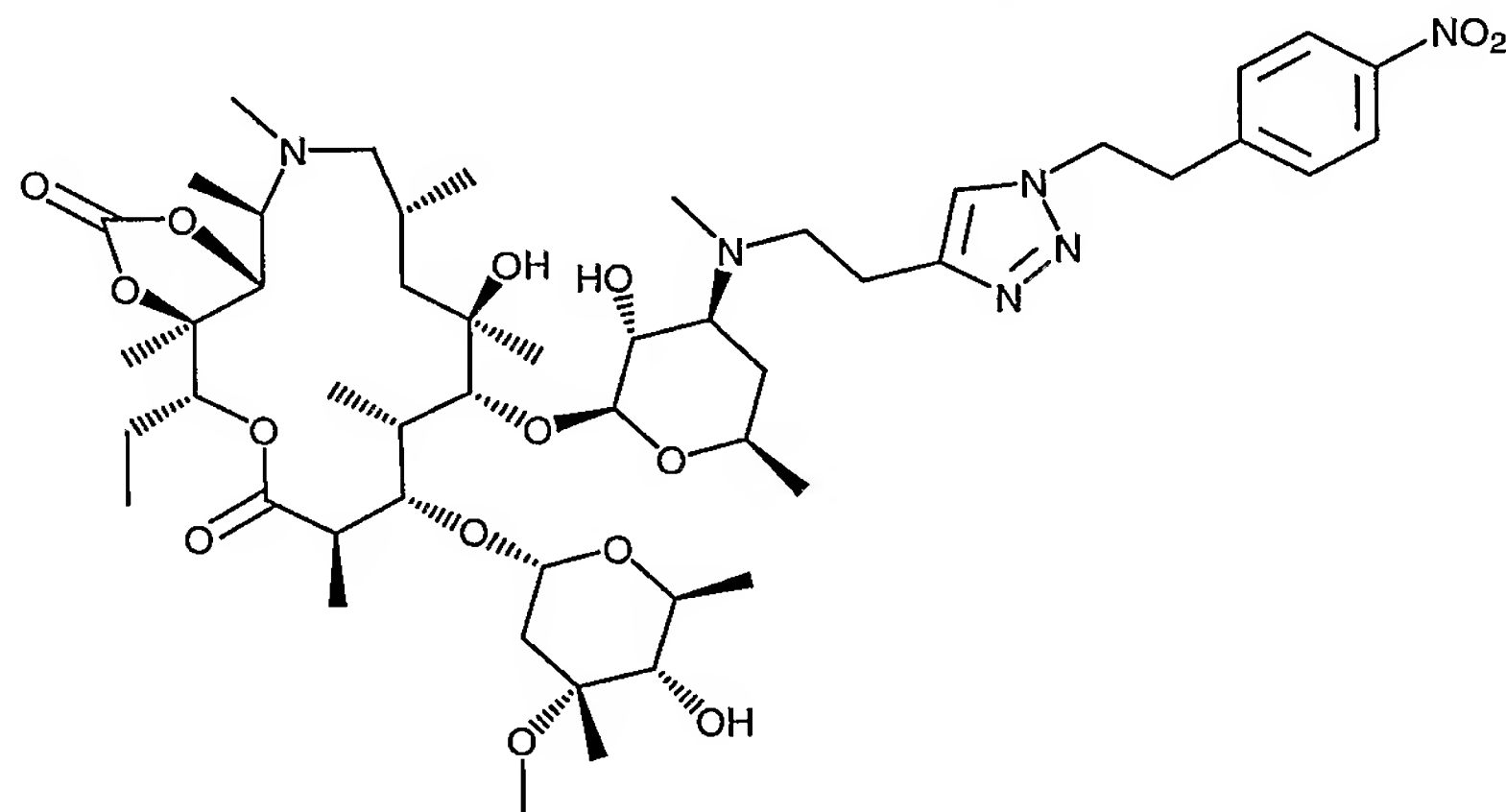
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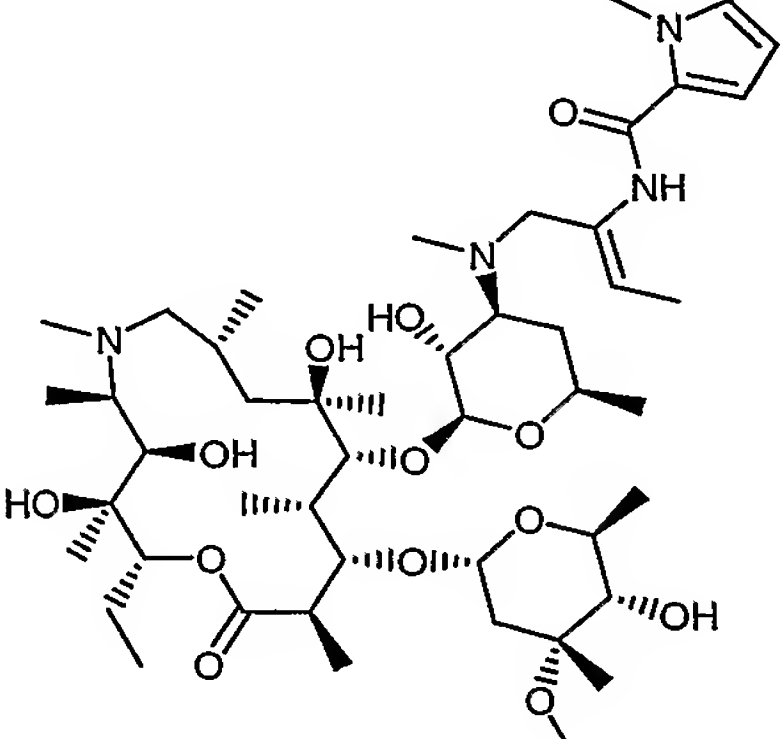
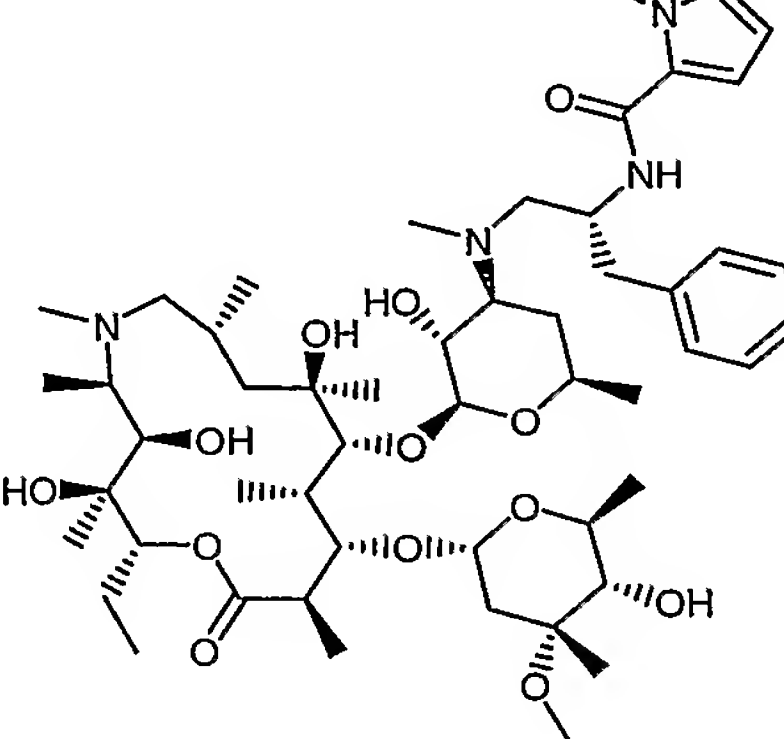
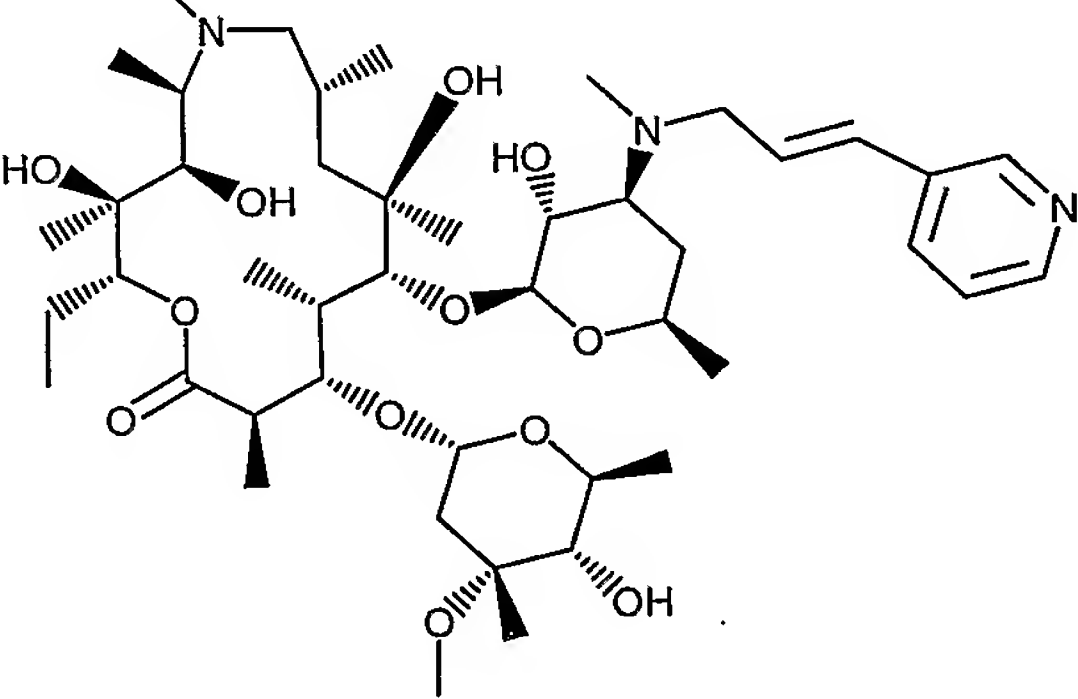
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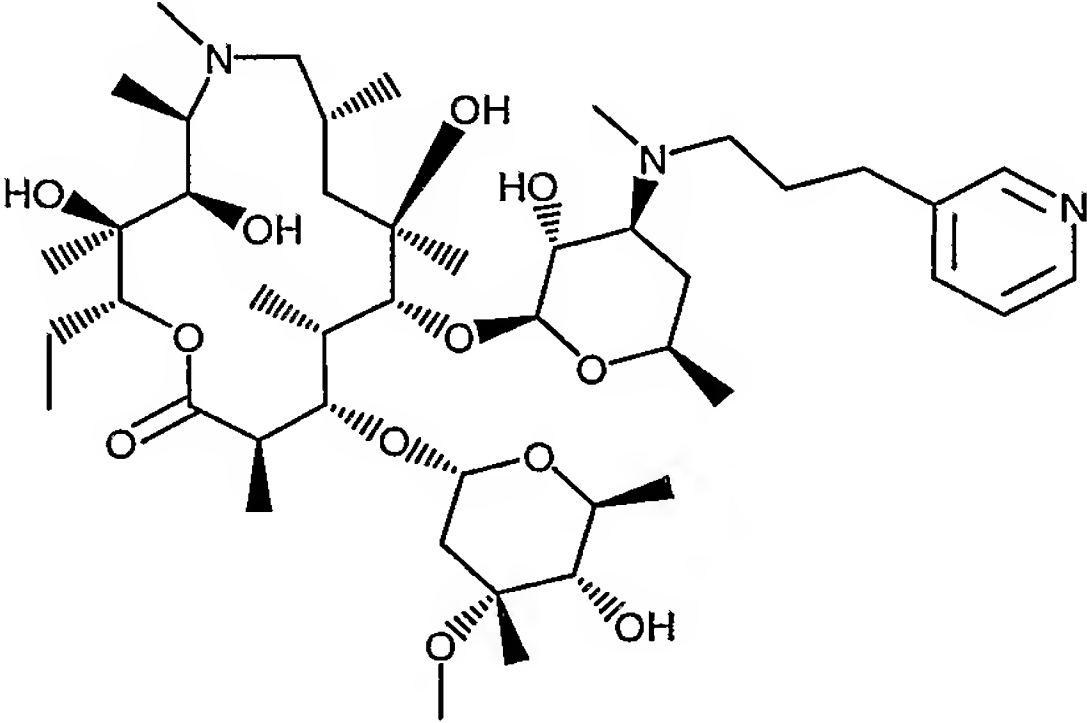
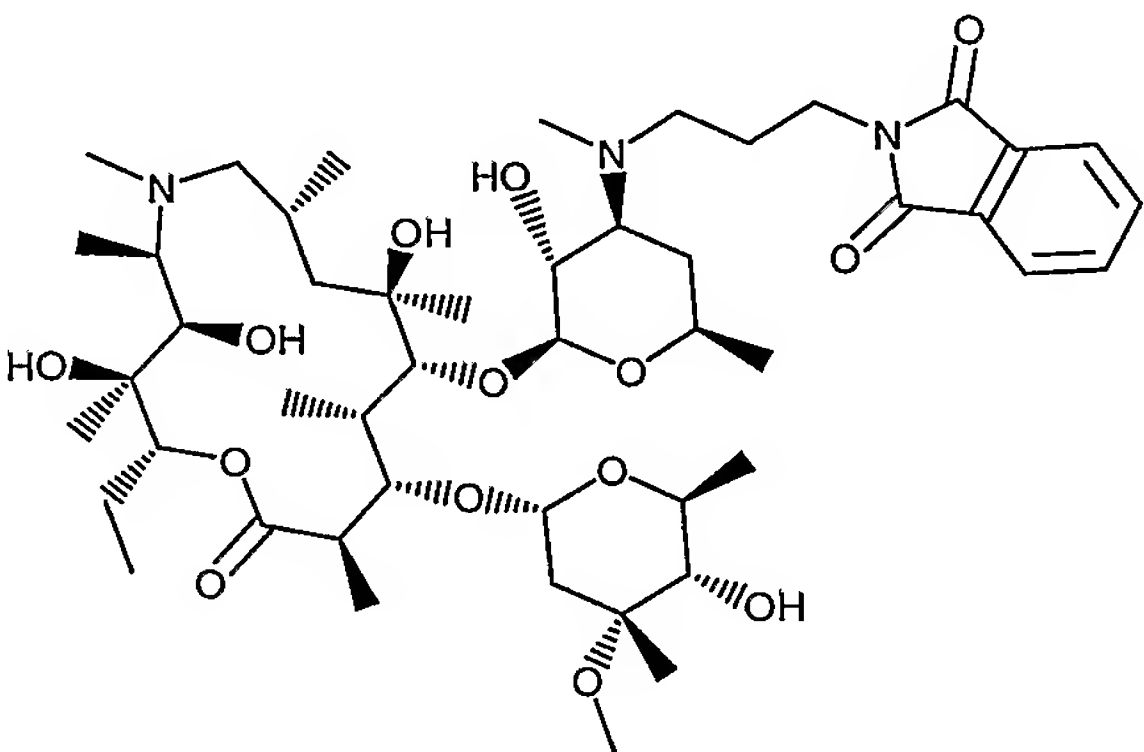
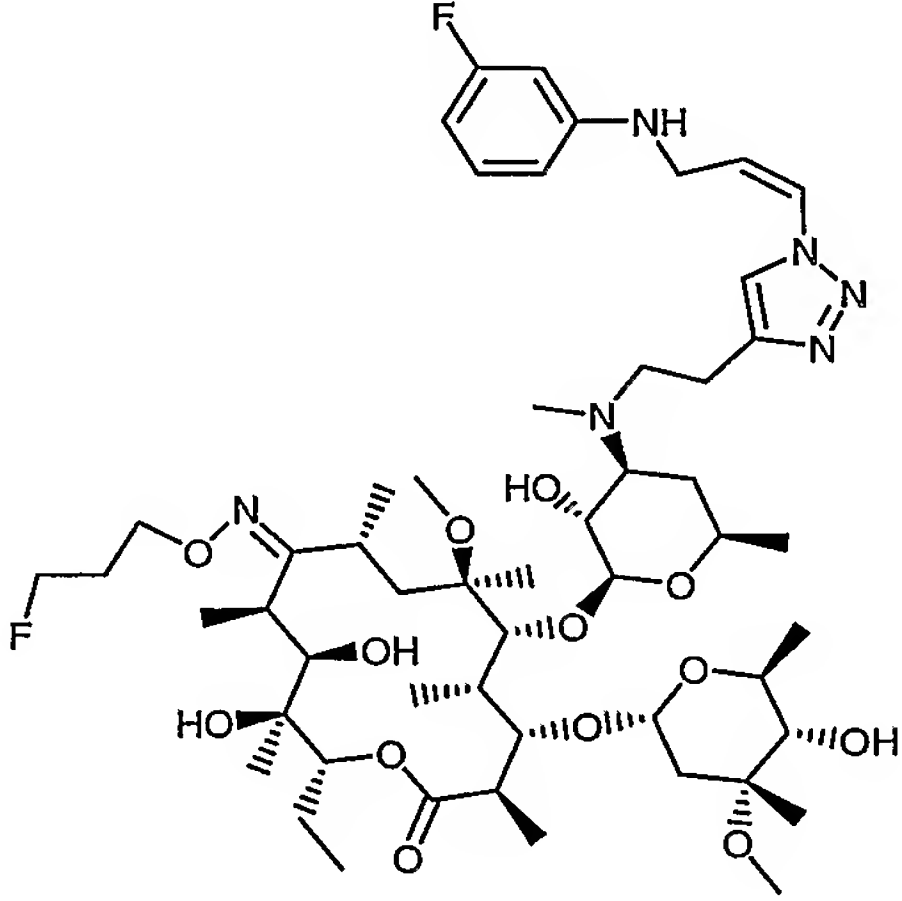
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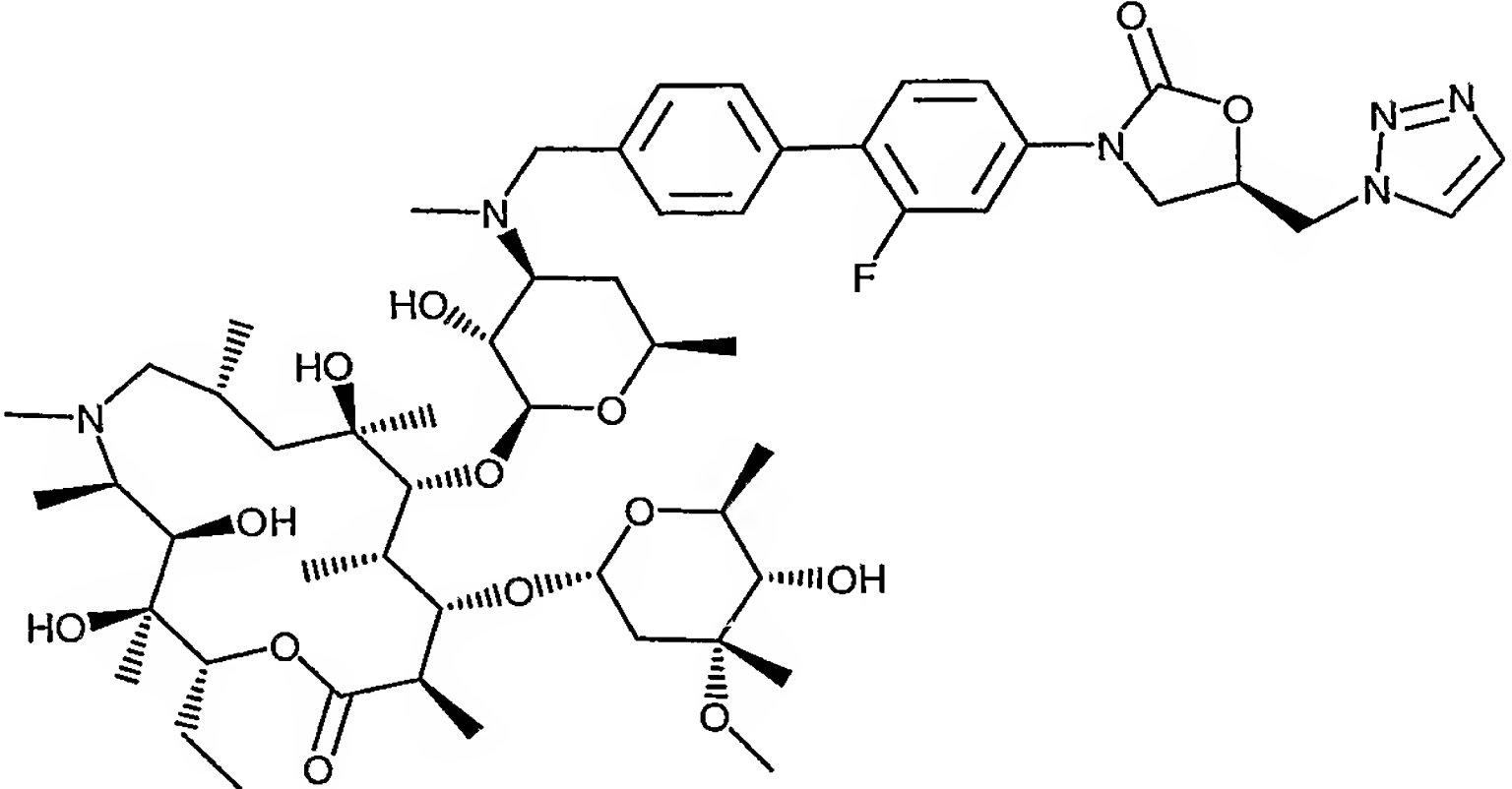
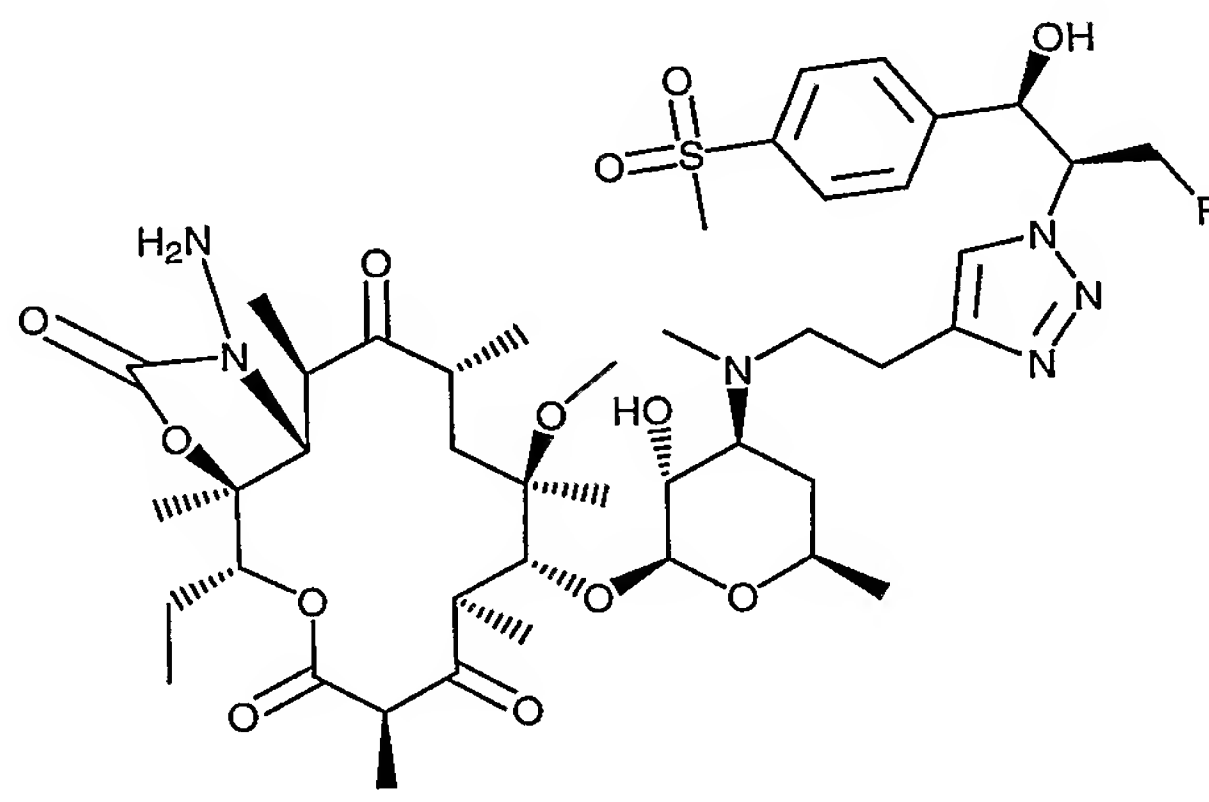
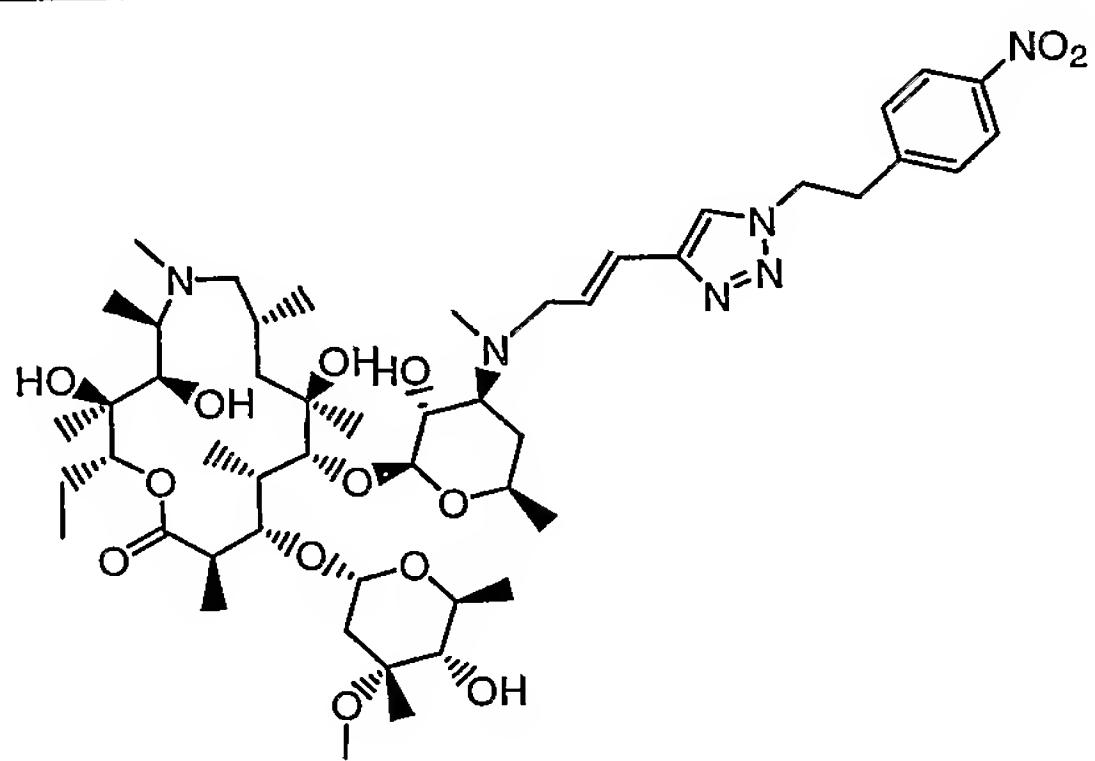
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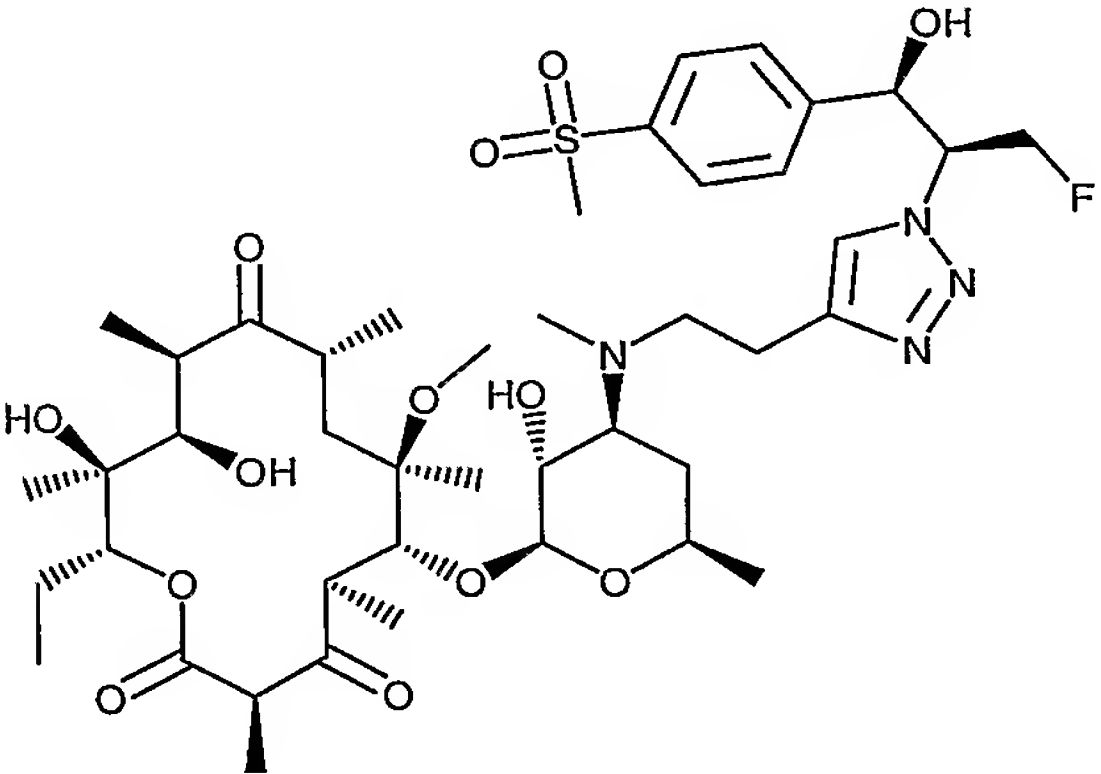
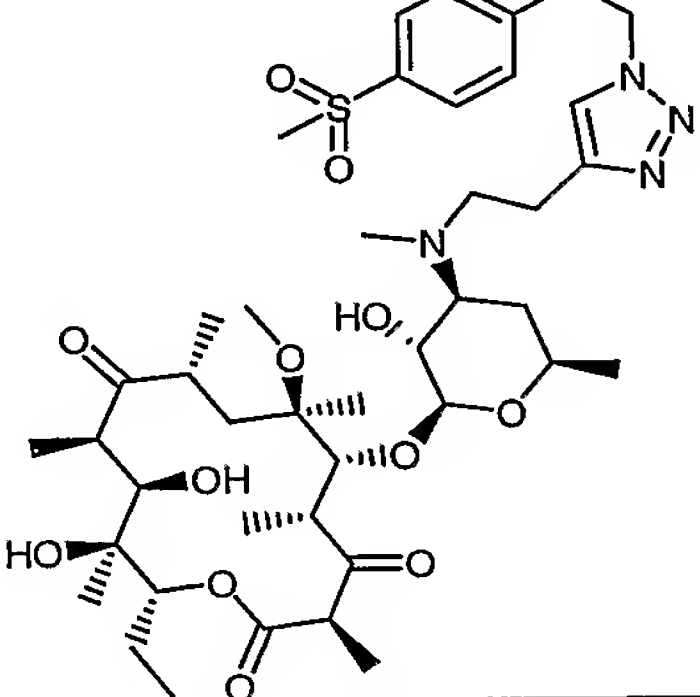
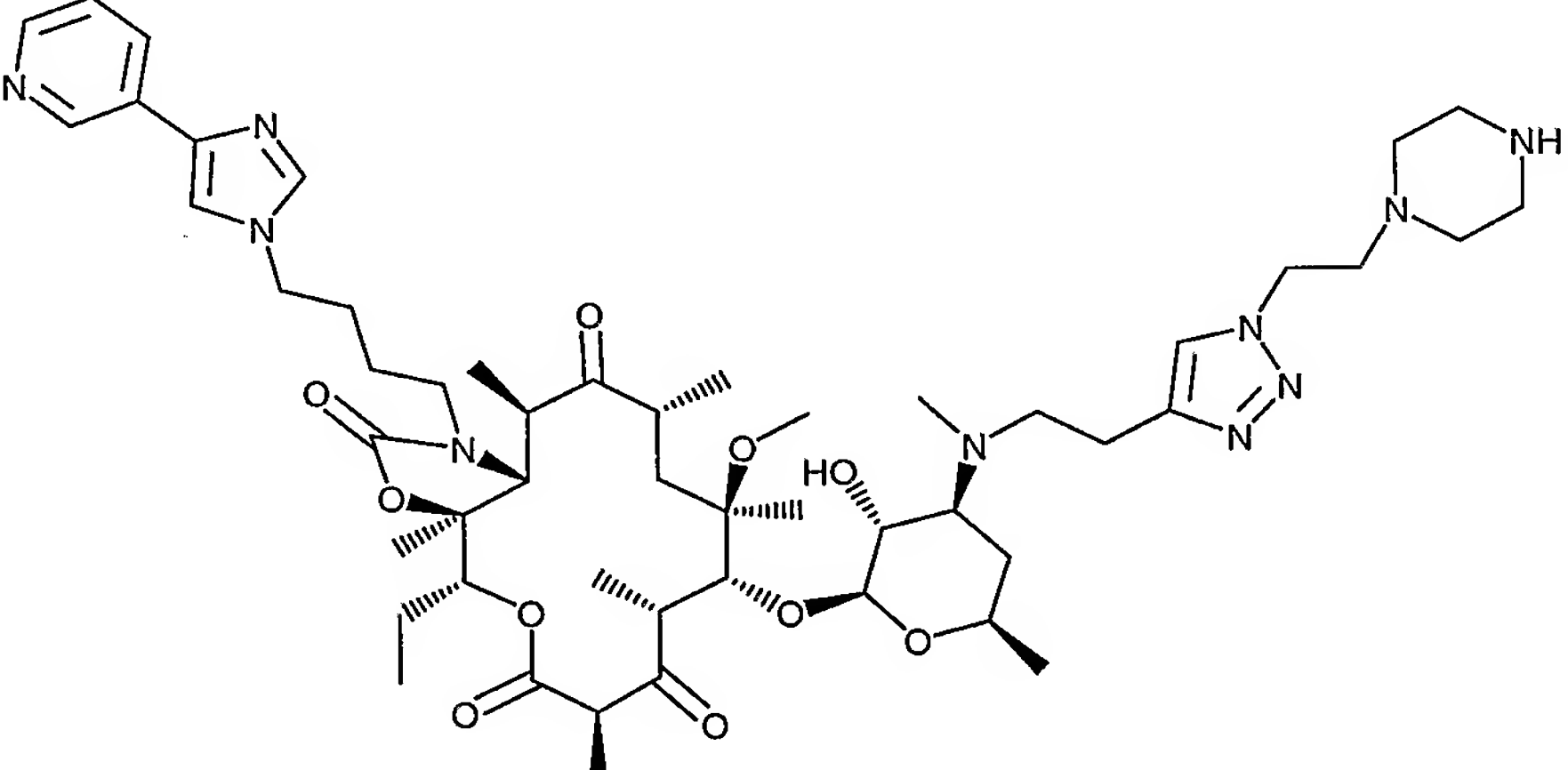
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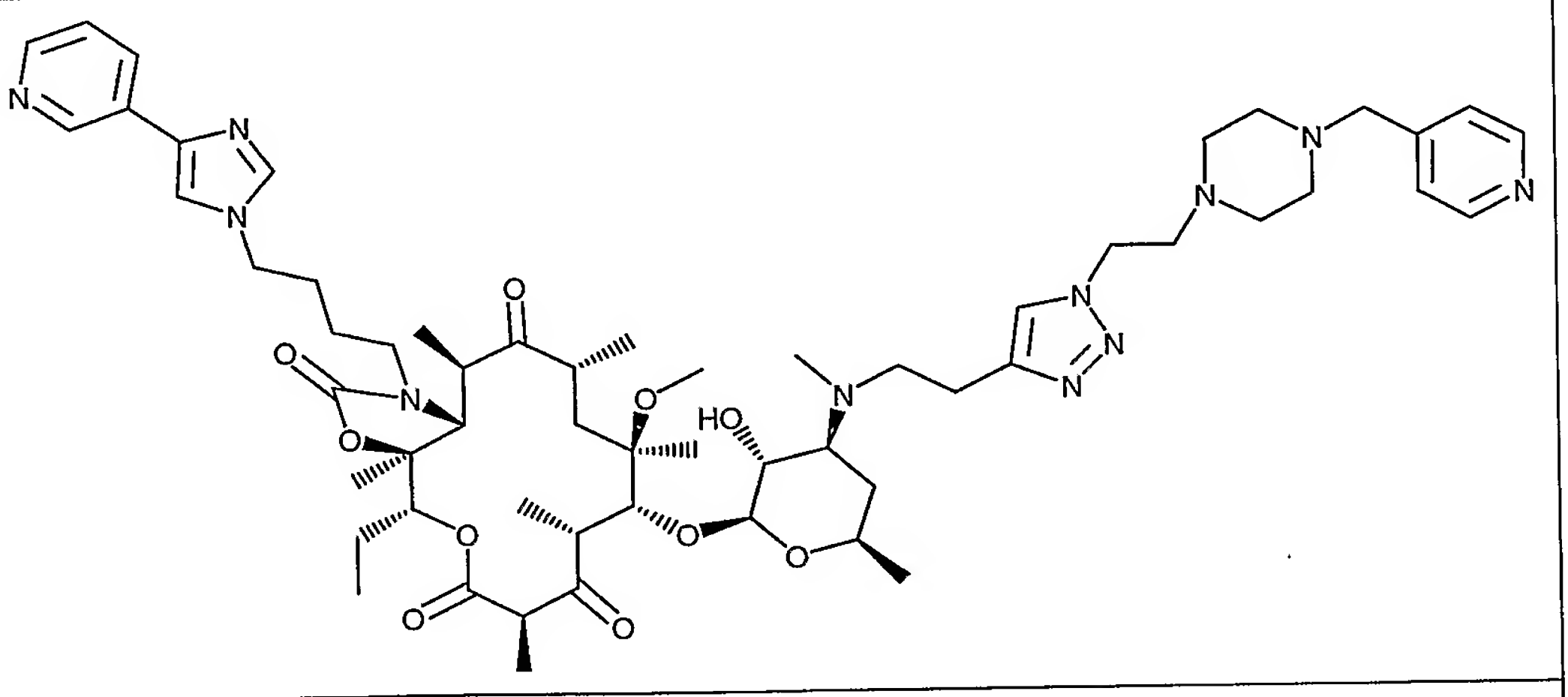
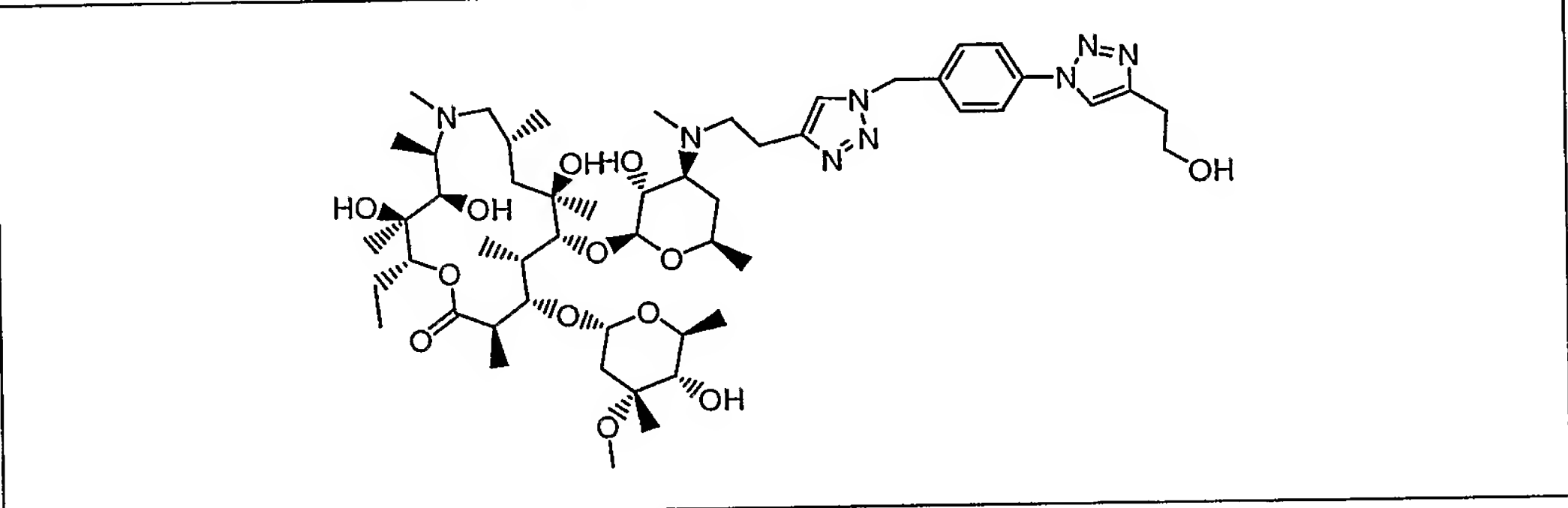
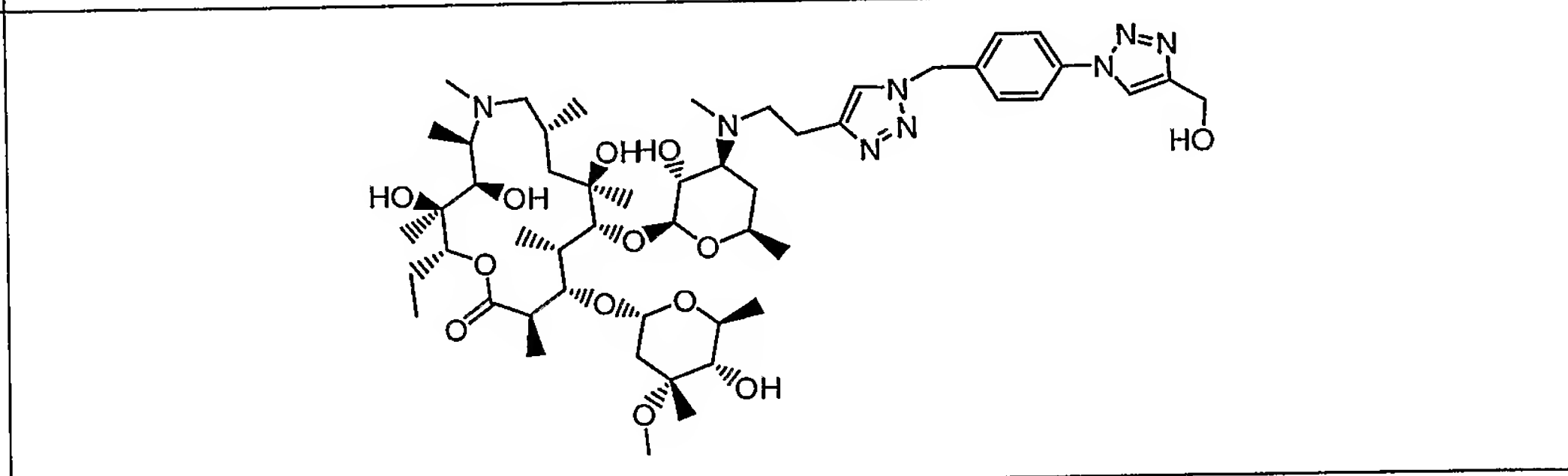
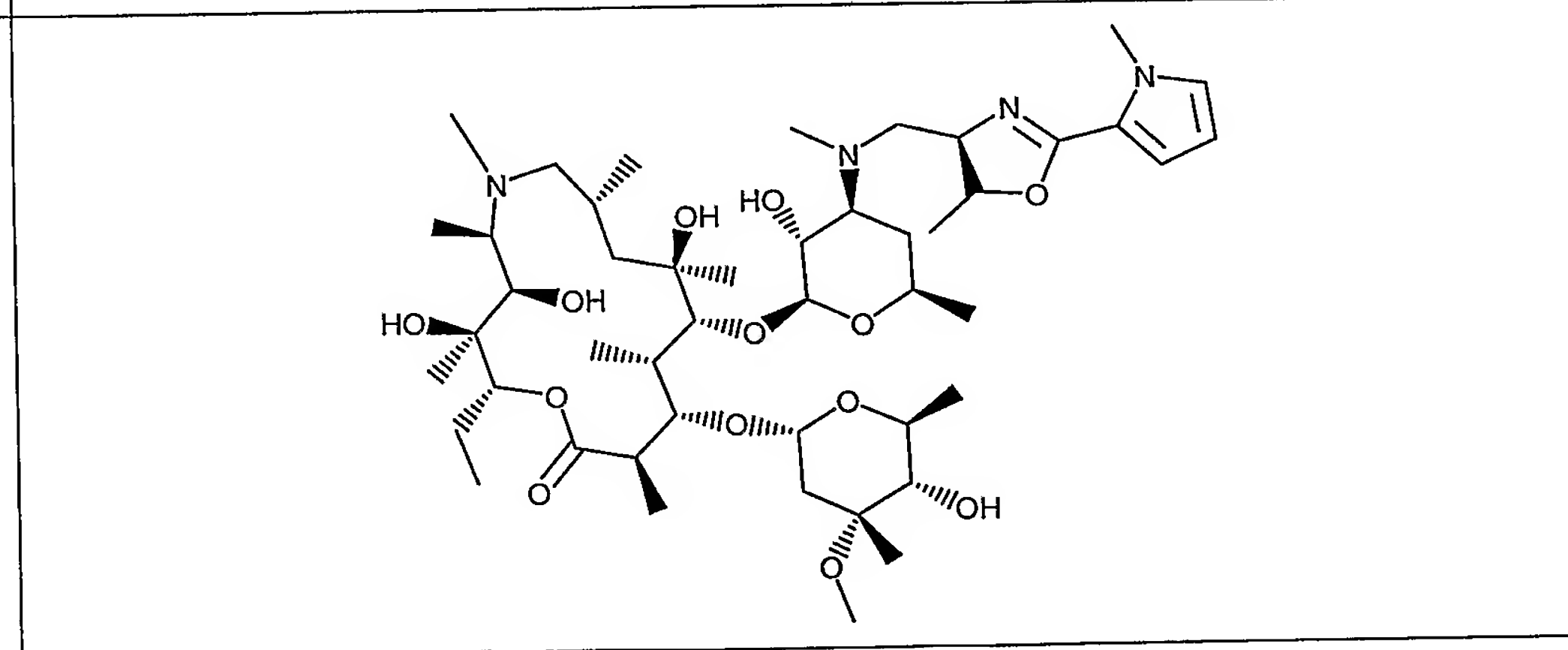
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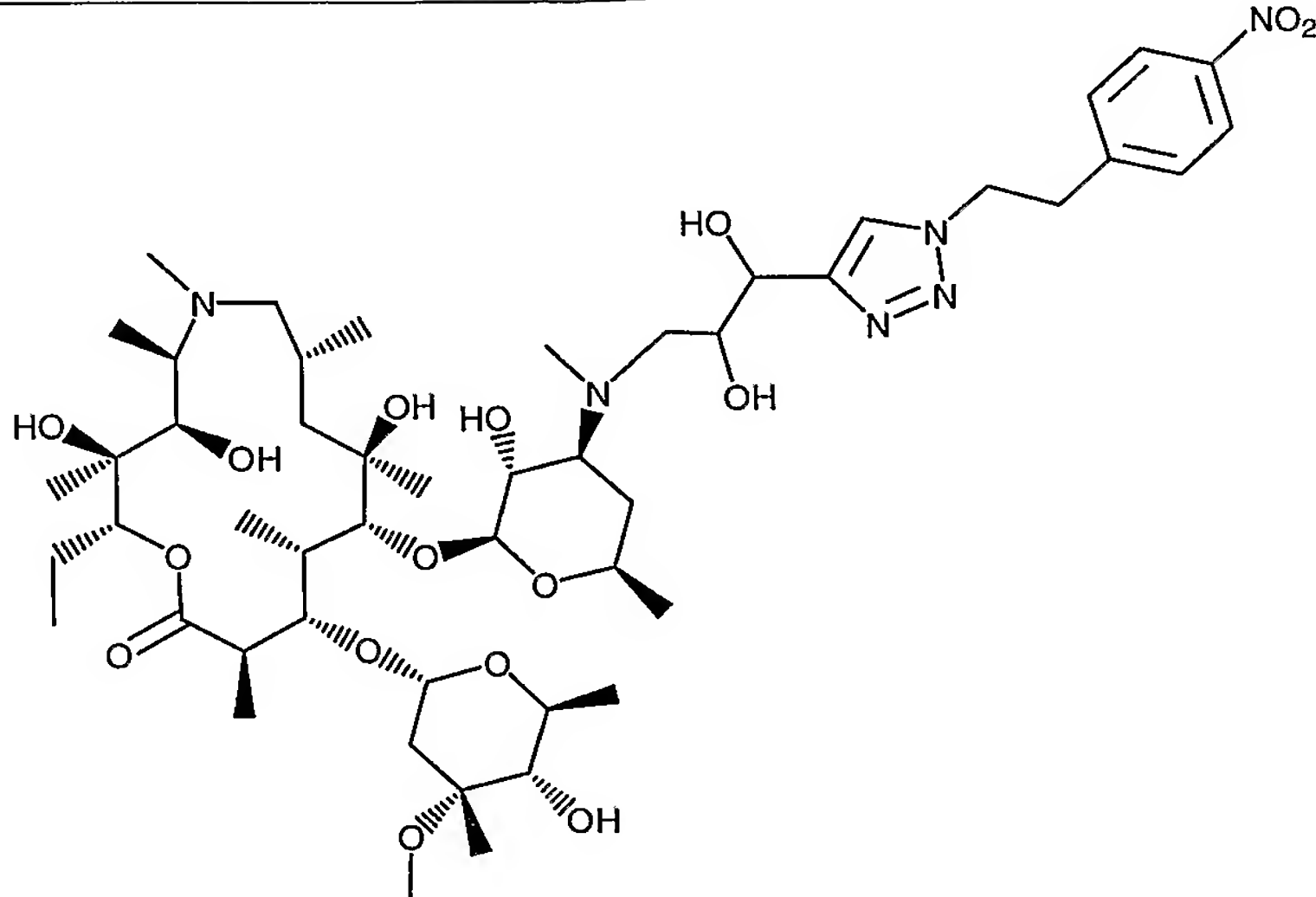
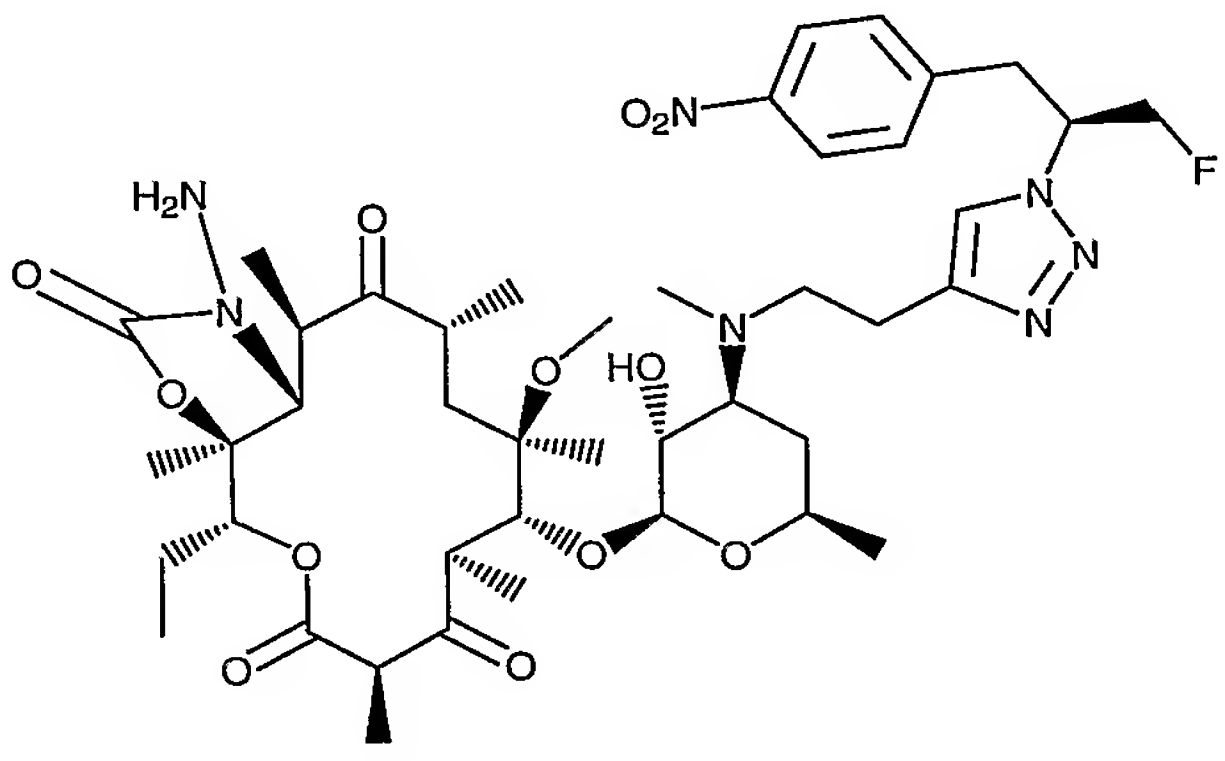
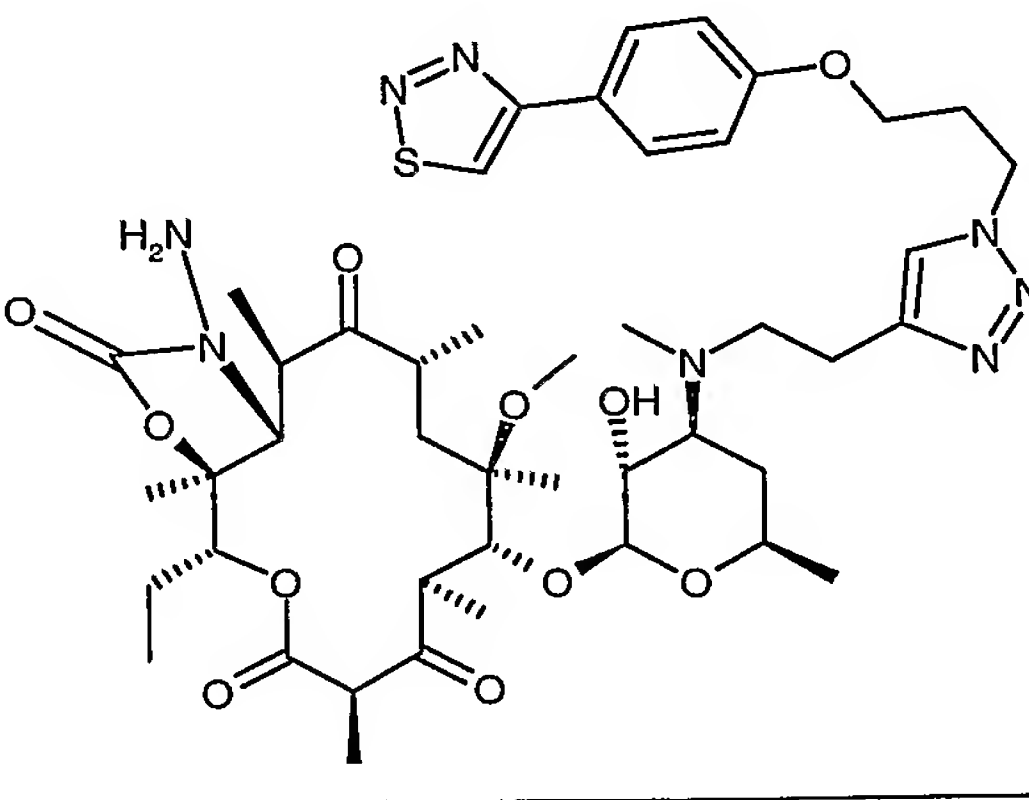
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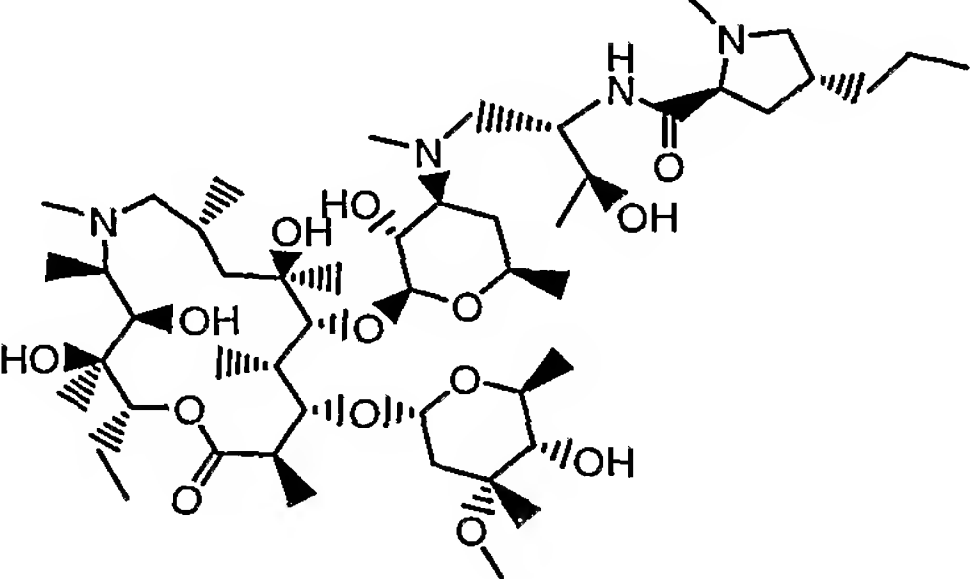
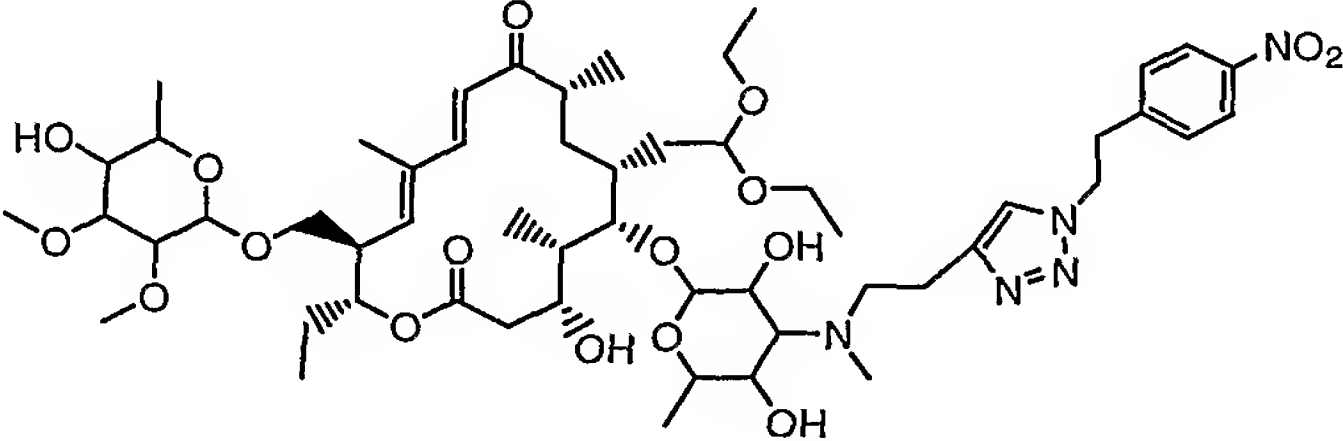
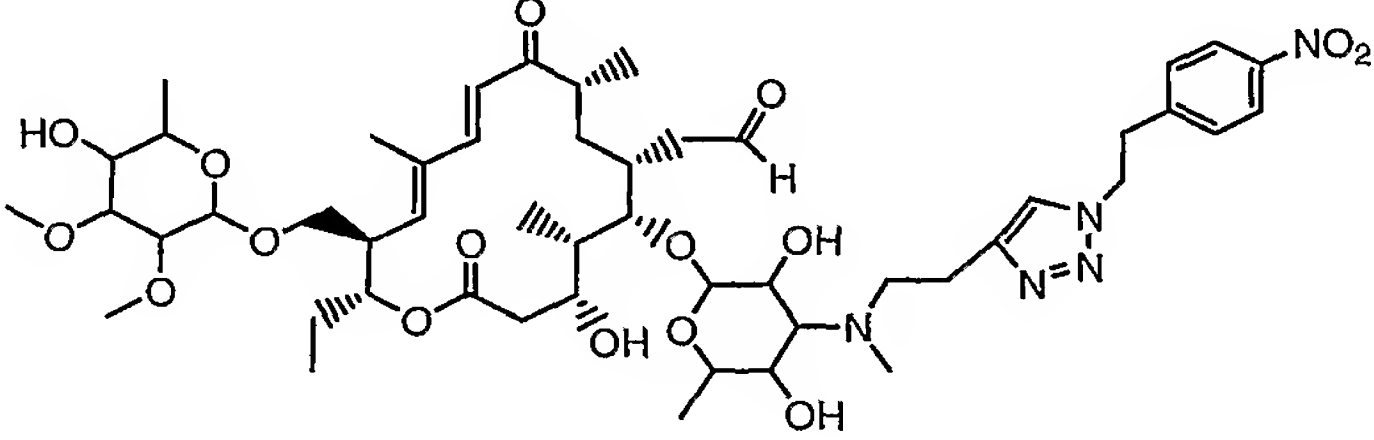
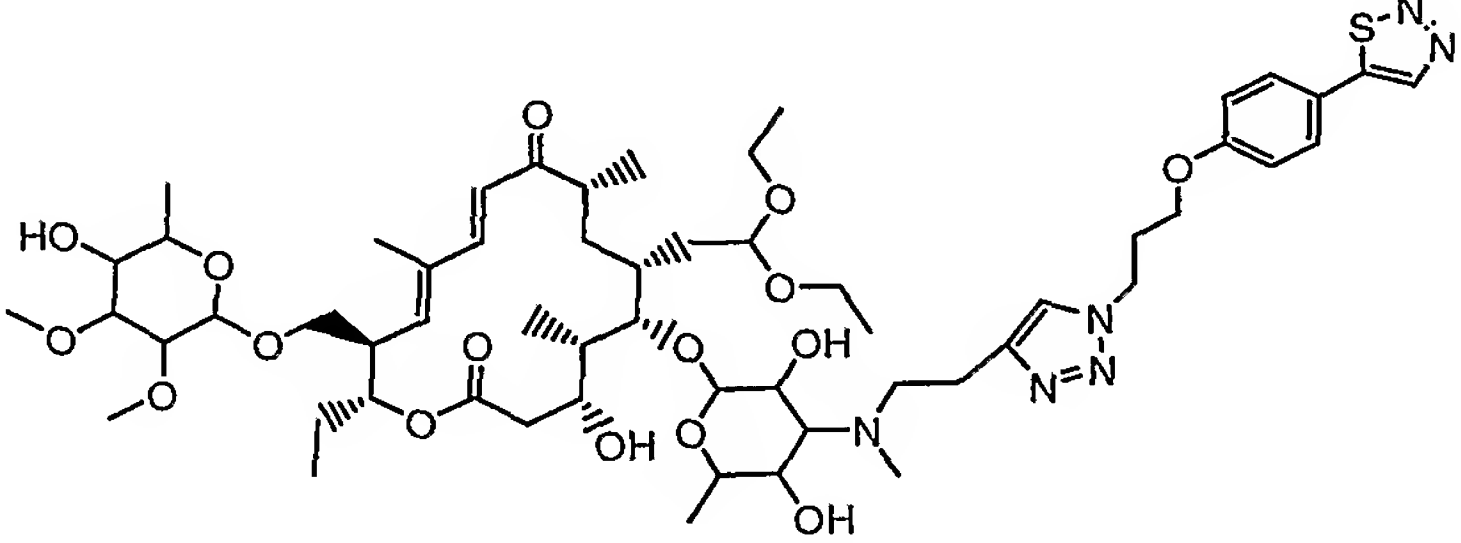
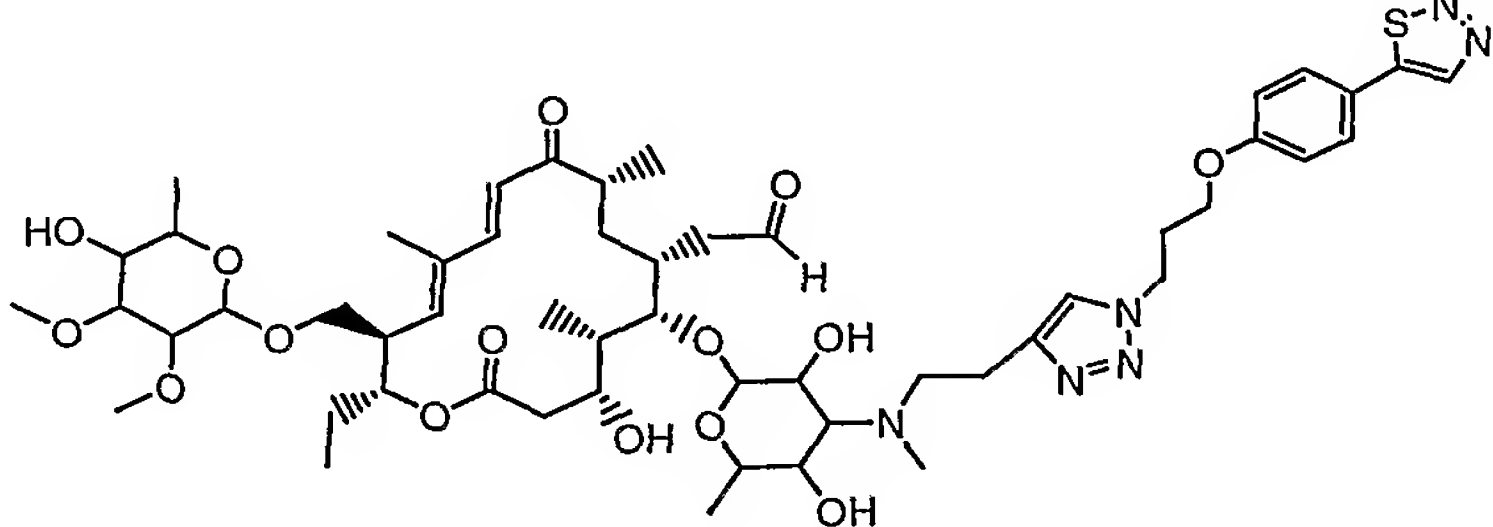
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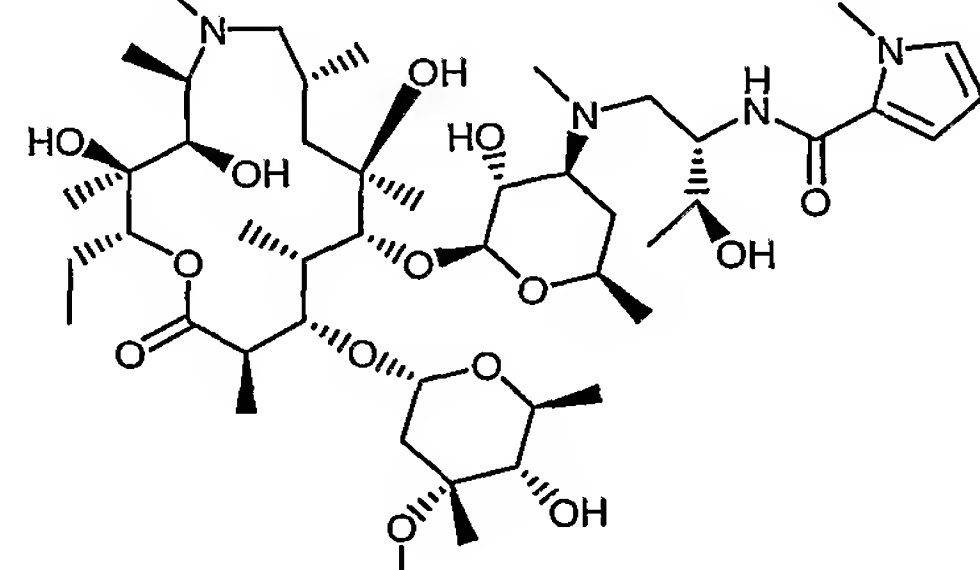
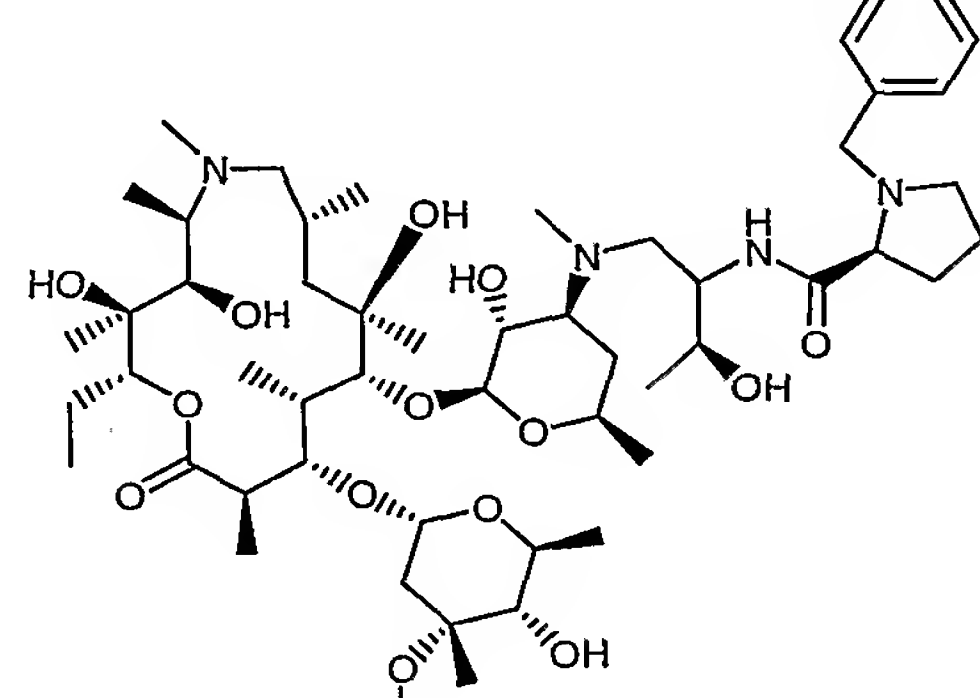
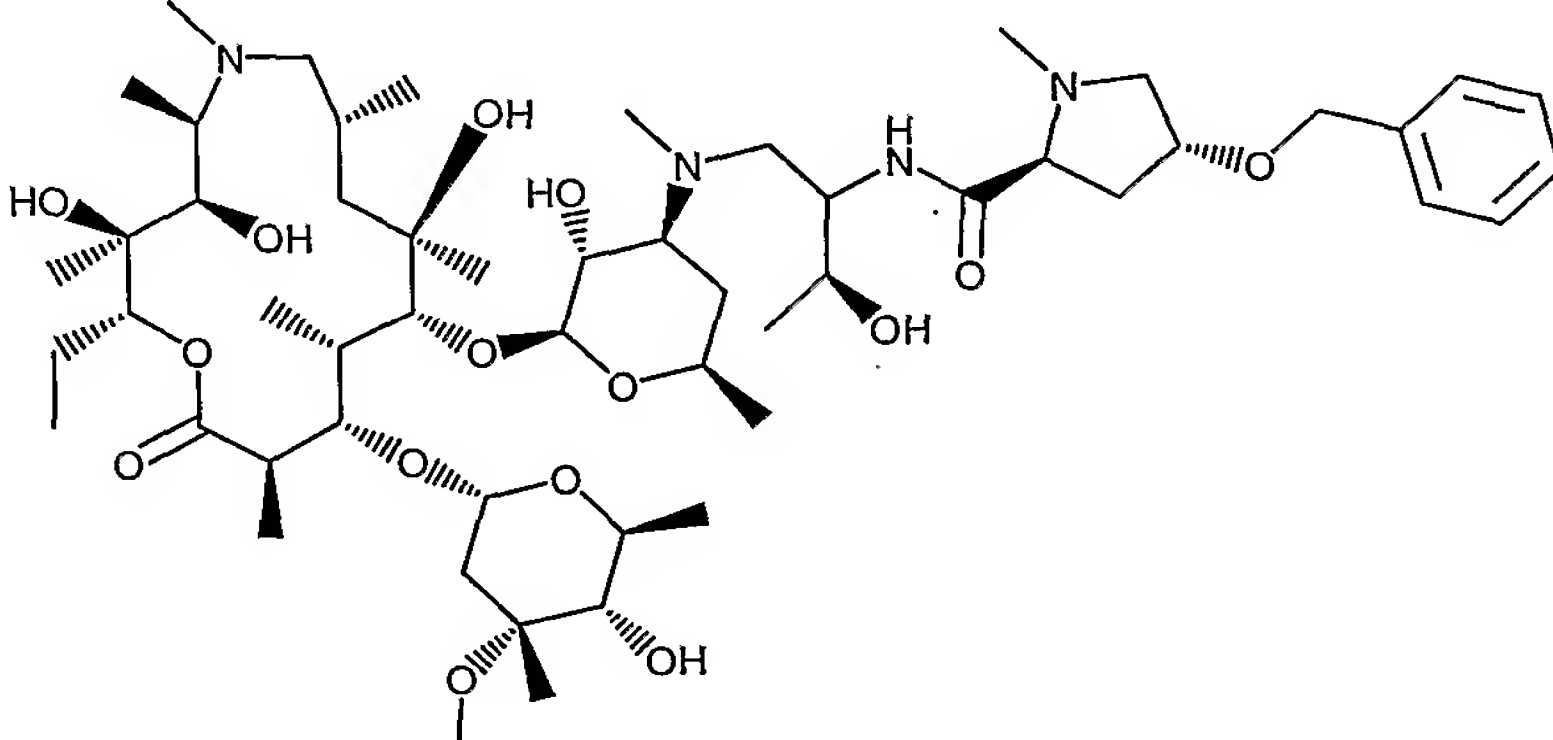
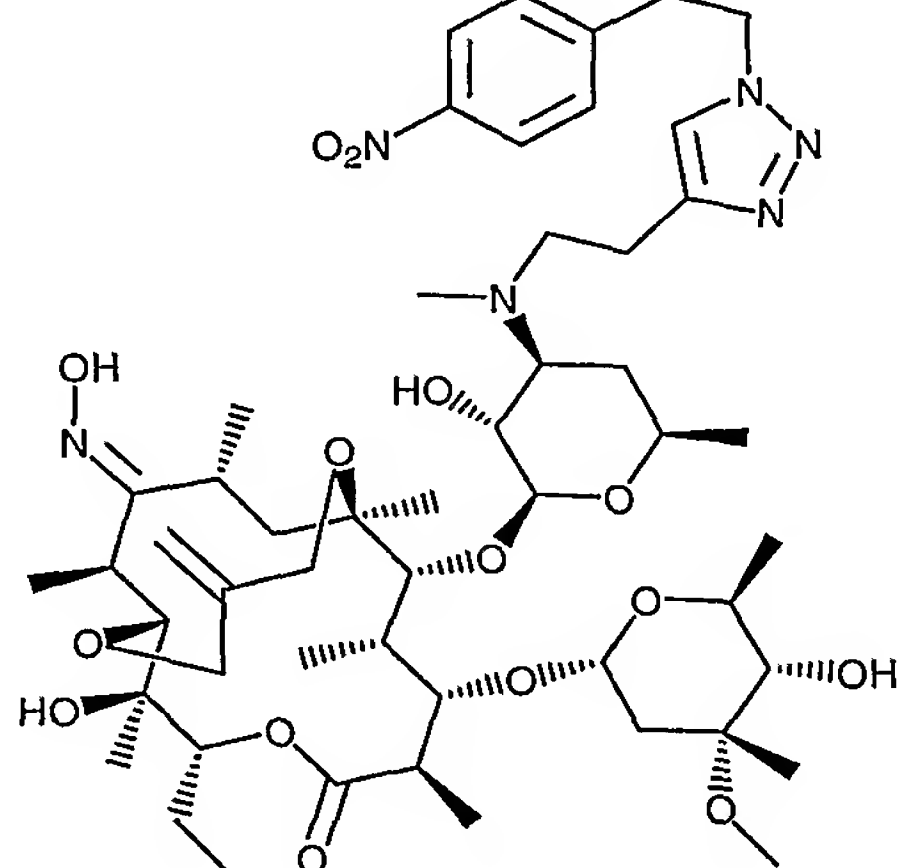
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619	 <p>Chemical structure 619 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups. A side chain is attached to the core, containing a triazole ring and a 4-nitrophenyl group. The structure is highly detailed with stereochemistry indicated by wedges and dashes.</p>
620	 <p>Chemical structure 620 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups. A side chain is attached to the core, containing a triazole ring and a 4-nitrophenyl group. The structure is highly detailed with stereochemistry indicated by wedges and dashes.</p>
621	 <p>Chemical structure 621 is a complex molecule. It features a central bicyclic core with multiple hydroxyl groups. A side chain is attached to the core, containing a triazole ring and a 4-nitrophenyl group. The structure is highly detailed with stereochemistry indicated by wedges and dashes.</p>

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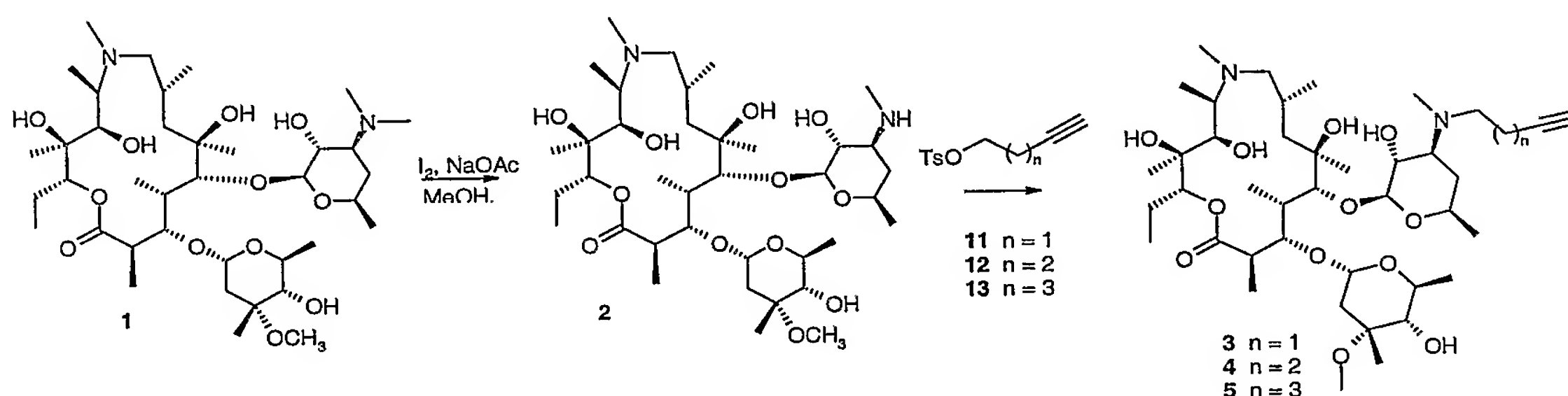
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Example 1 - Synthesis of Compounds 101-280

Schemes 100 and 101 below depict the synthesis of compounds **101-280**. Demethylation of azithromycin **1** selectively produced 3'-*N*-desmethylazithromycin **2**. Amine **2** was selectively alkylated with tosylates **11**, **12** and **13** to produce alkynes **3**, **4** and **5**, respectively. As shown in

25 Scheme 101 alkynes **3**, **4**, or **5** are reacted with azides **14a** – **14gm** in the presence of copper(I) iodide to selectively afford the triazoles **101-280**.

Scheme 100: Synthesis of alkynes 3, 4 and 5.**30 Synthesis of 3'-*N*-desmethylazithromycin 2**

Azithromycin **1** (0.80 grams (g), 1.02 millimoles (mmol)) and sodium acetate (NaOAc) (0.712 g, 8.06 mmol) were dissolved in 80% aqueous methanol (MeOH) (25 mL). The solution was heated to 50°C followed by addition of iodine (I_2) (0.272 g, 1.07 mmol) in three batches within 3 minutes. The reaction was maintained at a pH between 8 – 9 by adding 1N sodium hydroxide (NaOH) (1 mL) at 10 min and 45 minute intervals. The solution turned colorless

35 within 45 minutes (min), however, stirring was continued for 2 hours (hr). TLC (methylene chloride(CH_2Cl_2)/MeOH/ammonium chloride (NH_4OH) 10:1:0.05) after 2 hours showed a single major product ($R_f = 0.66$). The reaction was cooled to room temperature (rt), poured into H_2O (75 mL) containing NH_4OH (1.5 mL) and extracted with chloroform ($CHCl_3$) (3 x 30 mL). The

40 combined organic layers were washed with H_2O (30 mL) containing NH_4OH (1.5 mL), dried over Na_2SO_4 and the solvent evaporated to give a white residue. The crude was purified on a silica gel column eluting with CH_2Cl_2 /MeOH/ NH_4OH 18:1:0.05 to 10:1:0.05 to provide amine **2** (0.41 g, 55%).

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20 Synthesis of alkyne 5

A mixture of 3'-*N*-desmethylazithromycin **2** (0.5 g, 0.7 mmol) and tosylate **13** (0.20 g, 0.82 mmol) in *N,N*-diisopropylethylamine (Hunig's base) (3 mL) was stirred at 80°C for 4 hours. The reaction mixture was diluted to 50 mL with ethylacetate (EtOAc) and washed with NaHCO₃(aq) and with brine (1 x 30 mL). The organic layer was dried over K₂CO₃ and the
25 solvent was evaporated to give 0.65g of a yellow foam. The crude product was purified on silica gel column eluting with CH₂Cl₂/MeOH 40:1 to give **5** as a white solid (0.42 g, 74%).

Synthesis of alkyne 4

Alkyne **3** was made from 3'-*N*-desmethylazithromycin **2** and tosylate **12** using the same procedure described for the synthesis of compound **5**.

30

Synthesis of alkyne 3

Alkyne **3** was made from 3'-*N*-desmethylazithromycin **2** and tosylate **11** using the same procedure described for the synthesis of compound **5**.

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Table 2

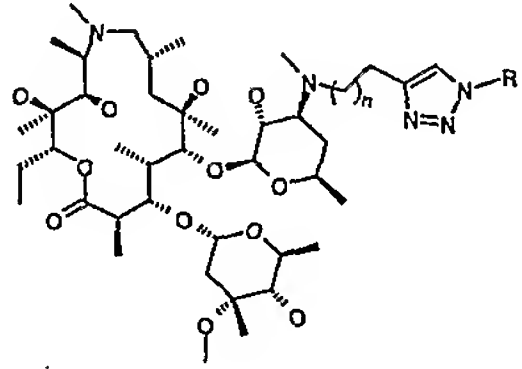
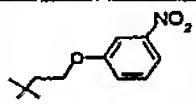
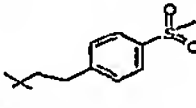
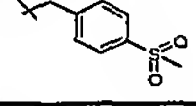
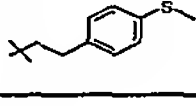
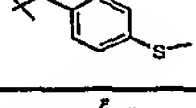
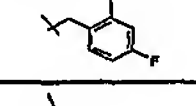
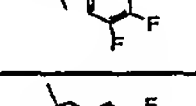
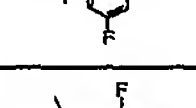
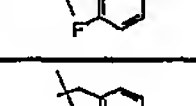
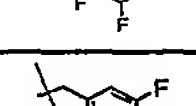
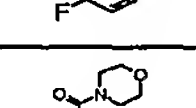
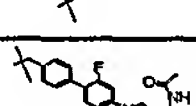
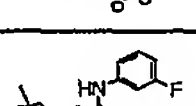
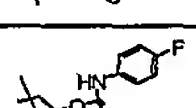
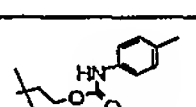
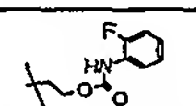
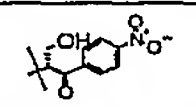
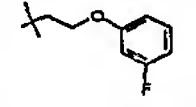
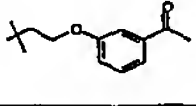

						
Compound	R	Azide	n	Alkyne	Yield	LCMS (M/Z)
101		14a	1	3	55%	ND
102		14b	1	3	62%	507.0 (M + 2H) ²⁺ 1012.9 (M + H) ⁺
103		14c	1	3	57%	500.1 (M + 2H) ²⁺ 998.9 (M + H) ⁺ 1020.9 (M + Na) ⁺
104		14d	1	3	67%	491.1 (M + 2H) ²⁺ 980.9 (M + H) ⁺ 1002.9 (M + Na) ⁺
105		14e	1	3	76%	484.1 (M + 2H) ²⁺ 966.9 (M + H) ⁺
106		14f	1	3	95%	504.0 (M + 2H) ²⁺ 1008.9 (M + H) ⁺
107		14g	1	3	79%	479.2 (M + 2H) ²⁺ 798.6 (M - C ₈ H ₁₅ O ₃ + H) ⁺ 956.9 (M
108		14h	1	3	93%	479.2 (M + 2H) ²⁺ 798.6 (M - C ₈ H ₁₅ O ₃ + H) ⁺ 956.8 (M
109		14i	1	3	79%	479.1 (M + 2H) ²⁺ 798.5 (M - C ₈ H ₁₅ O ₃ + H) ⁺ 956.7 (M
110		14k	1	3	97%	479.2 (M + 2H) ²⁺ 798.6 (M - C ₈ H ₁₅ O ₃ + H) ⁺ 956.8 (M
111		14l	1	3	97%	479.0 (M + 2H) ²⁺ 956.7 (M + H) ⁺
112		14m	1	3	49%	479.5 (M + 2H) ²⁺ 957.9 (M + H) ⁺
113		14n	1	3	30%	586.1 (M + 2H) ²⁺ 1171.1 (M + H) ⁺
114		14o	1	3	70%	506.6 (M + 2H) ²⁺
115		14p	1	3	88%	506.6 (M + 2H) ²⁺
116		14q	1	3	62%	504.6 (M + 2H) ²⁺
117		14r	1	3	78%	506.6 (M + 2H) ²⁺
118		14s	1	3	43%	513.6 (M + 2H) ²⁺
119		14t	1	3	51%	585.6 (M + 2H) ²⁺
120		14u	1	3	74%	497.3 (M + 2H) ²⁺

Table 2 continued

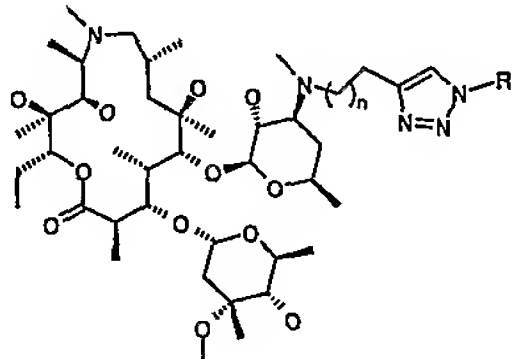
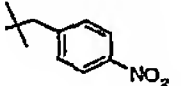
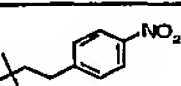
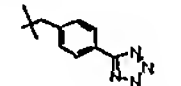
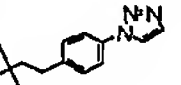
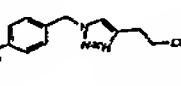
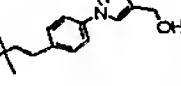
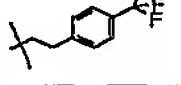
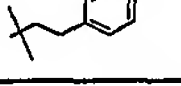
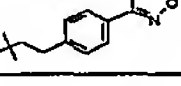
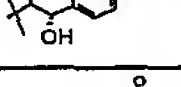
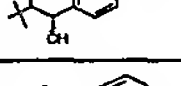
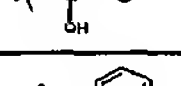
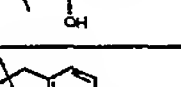

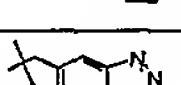


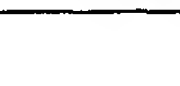
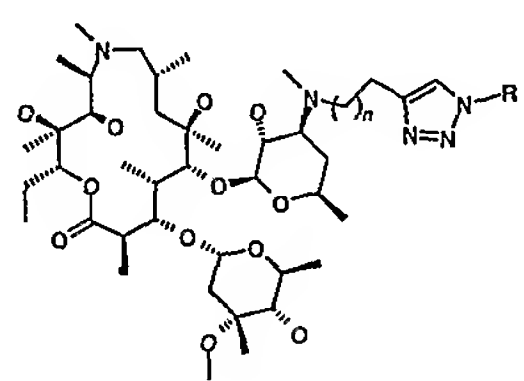
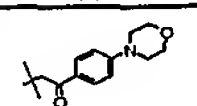
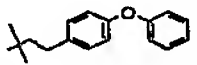
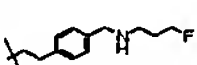
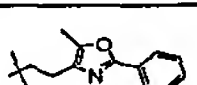
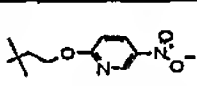
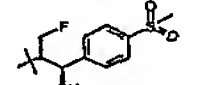
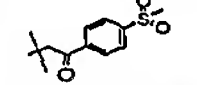
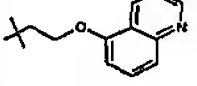
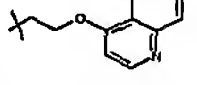
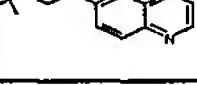
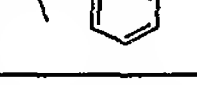
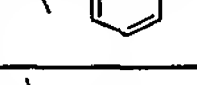
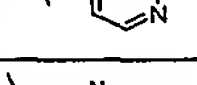
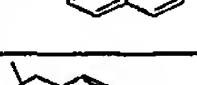
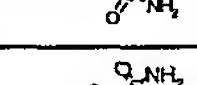

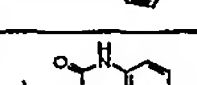
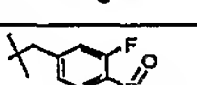
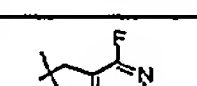
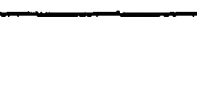
						
Compound	R	azide	n	Alkyne	Yield	LCMS (M/Z)
121		14v	1	3	47%	965.2 (M + H) ⁺ 987.1 (M + Na) ⁺
122		14w	1	3	96%	979.5 (M + H) ⁺ 1001.4 (M + Na) ⁺
123		14x	1	3	61%	988.4 (M + H) ⁺
124		14y	1	3	28%	1001.4 (M + H) ⁺ 1023.3 (M + Na) ⁺
125		14z	1	3	70%	1031.4 (M + H) ⁺
126		14aa	1	3	51%	1031.9 (M + H) ⁺
129		14ad	1	3	69%	1002.7 (M + H) ⁺ 1024.6 (M + Na) ⁺
130		14ae	1	3	73%	952.7 (M + H) ⁺ 974.7 (M + Na) ⁺
131		14af	1	3	85%	1016.9 (M + H) ⁺ 1038.9 (M + Na) ⁺
132		14ag	1	3	92%	514.1 (M + 2H) ²⁺
133		14ah	1	3	38%	530.1 (M + 2H) ²⁺
134		14ai	1	3	39%	483.2 (M + 2H) ²⁺
135		14aj	1	3	37%	483.1 (M + 2H) ²⁺
136		14ak	1	3	60%	494.6 (M + 2H) ²⁺
137		14al	1	3	67%	494.1 (M + 2H) ²⁺
138		14am	1	3	81%	488.6 (M + 2H) ²⁺ 975.8 (M + H) ⁺
139		14an	1	3	67%	503.1 (M + 2H) ²⁺
140		14ao	1	3	74%	526.1 (M + 2H) ²⁺

Table 2 continued

						
Compound	R	azide	n	3	Yield	LCMS (M/Z)
141		14ap	1	3	46%	517.7 (M + 2H) ²⁺ 1034.0 (M + H) ⁺
142		14aq	1	3	79%	514.1 (M + 2H) ²⁺
143		14ar	1	3	59%	512.6 (M + 2H) ²⁺
144		14as	1	3	94%	508.6 (M + 2H) ²⁺ 1015.9 (M + H) ⁺
145		14at	1	3	80%	499.0 (M + 2H) ²⁺
146		14au	1	3	35%	531.2 (M + 2H) ²⁺
147		14av	1	3	32%	514.3 (M + 2H) ²⁺
148		14aw	1	3	69%	501.2 (M + 2H) ²⁺
149		14ax	1	3	87%	501.1 (M + 2H) ²⁺
150		14ay	1	3	50%	501.4 (M + 2H) ²⁺
151		14az	1	3	62%	461.4 (M + 2H) ²⁺
152		14ba	1	3	42%	461.2 (M + 2H) ²⁺
153		14bb	1	3	45%	461.0 (M + 2H) ²⁺
154		14bc	1	3	66%	486.4 (M + 2H) ²⁺
155		14bd	1	3	93%	500.5 (M + 2H) ²⁺
156		14be	1	3	88%	507.4 (M + 2H) ²⁺
157		14bf	1	3	62%	493.7 (M + 2H) ²⁺ 987.2 (M + H) ⁺
158		14bg	1	3	70%	509.9 (M + 2H) ²⁺ 1018.3 (M + H) ⁺
159		14bh	1	3	37%	509.7 (M + 2H) ²⁺ 1017.9 (M + H) ⁺
160		14bi	1	3	75%	470.6 (M + 2H) ²⁺

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Table 2 continued

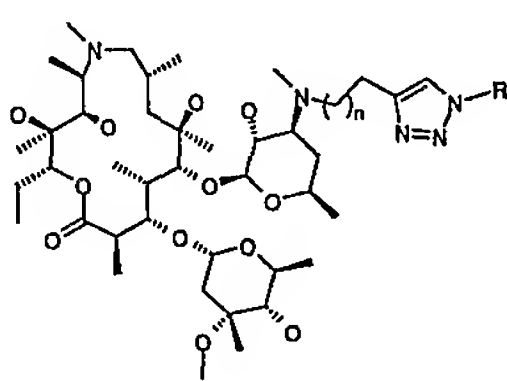
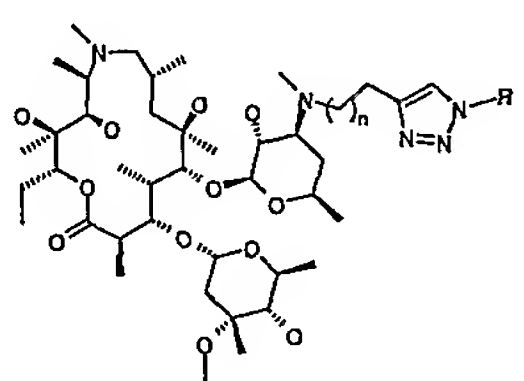
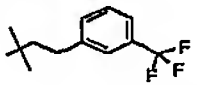
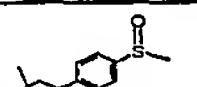
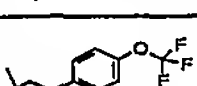
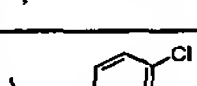
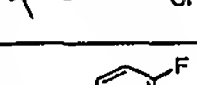
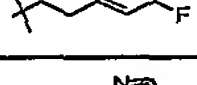
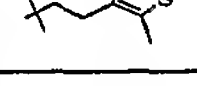
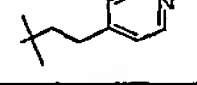
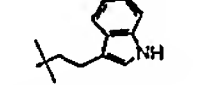
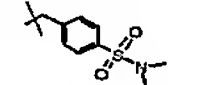
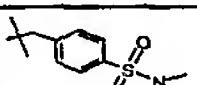
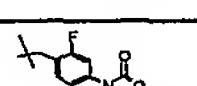
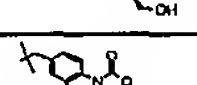
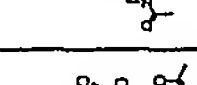
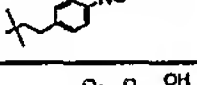
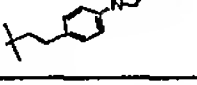
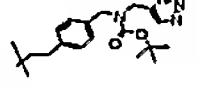
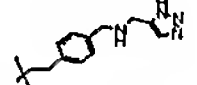
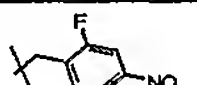
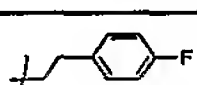
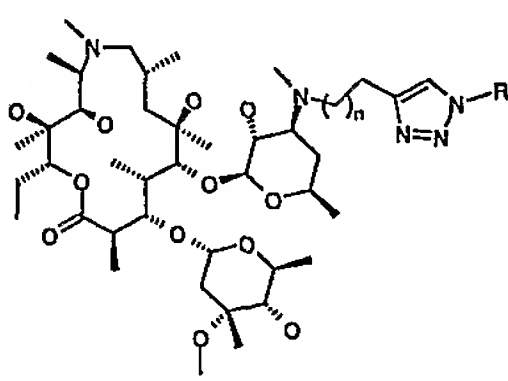
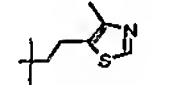
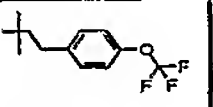
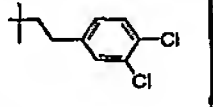
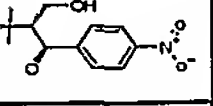
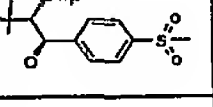
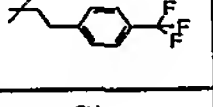
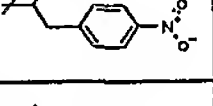
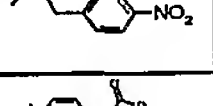

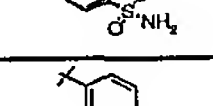
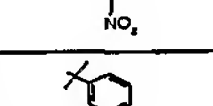
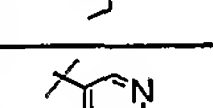
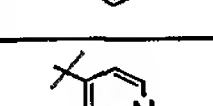

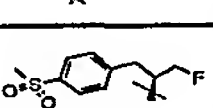
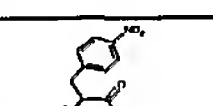
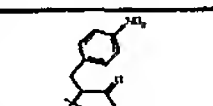
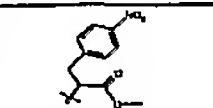
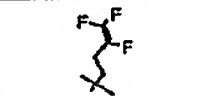

						
Compound	R	azide	n	Alkyne	Yield	LCMS (M/Z)
161		14bj	1	3	82%	496.6 (M + 2H) ²⁺ 991.9 (M + H) ⁺
162		14bk	1	3	69%	489.1 (M + 2H) ²⁺
163		14bl	1	3	57%	515.5 (M + 2H) ²⁺ 1029.9 (M + H) ⁺
164		14bm	1	3	57%	509.6 (M + 2H) ²⁺ 1017.8 (M + H) ⁺
165		14bn	1	3	63%	496.7 (M + 2H) ²⁺
166		14bo	1	3	89%	482.1 (M + 2H) ²⁺
167		14bp	1	3	90%	489.5 (M + 2H) ²⁺ 977.9 (M + H) ⁺
168		14bq	1	3	83%	505.6 (M + 2H) ²⁺ 1009.9 (M + H) ⁺ 1031.9 (M + Na) ⁺
169		14br	1	3	89%	497.6 (M + 2H) ²⁺
170		14bs	1	3	81%	504.5 (M + 2H) ²⁺
171		14bt	1	3	84%	506.6 (M + 2H) ²⁺
172		14bu	1	3	91%	497.6 (M + 2H) ²⁺
173		14bv	1	3	93%	490.6 (M + 2H) ²⁺ 979.9 (M + H) ⁺
174		14bw	1	3	96%	505.6 (M + 2H) ²⁺ 995.99 (M + H) ⁺ 1017.9 (M + Na) ⁺
175		14bx	1	3	97%	486.5 (M + 2H) ²⁺ 972.0 (M + H) ⁺
176		14bz	1	3	70%	522.4 (M + 2H) ²⁺ 1043.4 (M + H) ⁺
177		14ca	1	3	55%	482.2 (M + 2H) ²⁺ 963.5 (M + H) ⁺
178		14cb	1	3	88%	514.3 (M + 2H) ²⁺ 1027.5 (M + H) ⁺
179		14cc	1	3	94%	498.0 (M + 2H) ²⁺ 1016.7 (M + Na) ⁺
180		14cd	1	3	82%	489.5 (M + 2H) ²⁺ 977.6 (M + H) ⁺

Table 2 continued

						
Compound	R	azide	n	Alkyne	Yield	LCMS (M/Z)
181		14ce	1	3	83%	501.9 (M + 2H) ²⁺ 1002.7 (M + H) ⁺
182		14cf	1	3	90%	499.1 (M + 2H) ²⁺ 996.7 (M + H) ⁺
183		14cg	1	3	79%	510.0 (M + 2H) ²⁺ 1018.8 (M + H) ⁺ 1040.8 (M + Na) ⁺
184		14ch	1	3	93%	502.7 (M + 2H) ²⁺ 1002.7 (M + H) ⁺ 1024.7 (M + Na) ⁺
185		14ci	1	3	54%	486.0 (M + 2H) ²⁺ 970.8 (M + H) ⁺ 992.8 (M + Na) ⁺
186		14cj	1	3	91%	478.5 (M + 2H) ²⁺ 955.7 (M + H) ⁺
187		14ck	1	3	40%	468.3 (M + 2H) ²⁺ 935.9 (M + H) ⁺
188		14cl	1	3	72%	487.5 (M + 2H) ²⁺ 973.9 (M + H) ⁺
189		14cm	1	3	75%	514.6 (M + 2H) ²⁺ 1027.8 (M + H) ⁺
190		14cn	1	3	98%	507.4 (M + 2H) ²⁺ 1013.8 (M + H) ⁺
191		14co	1	3	89%	527.6 (M + 2H) ²⁺ 1053.8 (M + H) ⁺ 1075.9 (M + Na) ⁺
192		14cp	1	3	85%	548.1 (M + 2H) ²⁺ 1094.1 (M + H) ⁺
193		14cq	1	3	92%	546.9 (M + 2H) ²⁺ 1092.0 (M + H) ⁺
194		14cr	1	3	88%	525.8 (M + 2H) ²⁺ 1049.9 (M + H) ⁺
195		14cs	1	3	87%	573.3 (M + 2H) ²⁺
196		14ct	1	3	58%	523.2 (M + 2H) ²⁺
197		14cu	1	3	75%	492.6 (M + 2H) ²⁺
198		14ae	2	4	83%	484.0 (M + 2H) ²⁺ 966.6 (M + H) ⁺
199		14cf	2	4	79%	506.1 (M + 2H) ²⁺ 1010.7 (M + H) ⁺
200		14ci	2	4	87%	493.0 (M + 2H) ²⁺

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Table 2 continued

						
Compound	R	azide	n	Alkyne	Yield	LCMS (M/Z)
201		14cj	2	4	83%	485.5 (M + 2H) ²⁺ 969.6 (M + H) ⁺
202		14cg	2	4	83%	516.7 (M + 2H) ²⁺ 1032.8 (M + H) ⁺
203		14ch	2	4	87%	509.7 (M + 2H) ²⁺ 1016.7 (M + H) ⁺
204		14s	2	4	21%	1040.5 (M + H) ⁺
205		14cv	2	4	63%	1076.6 (M + H) ⁺
206		14ad	2	4	84%	1016.7 (M + H) ⁺ 1038.7 (M + Na) ⁺
207		14bq	2	4	93%	512.5 (M + 2H) ²⁺
208		14w	2	4	93%	497.6 (M + 2H) ²⁺ 994.4 (M + H) ⁺
209		14cx	3	5	88%	534.8 (M + 2H) ²⁺ 909.8 (M - C ₈ H ₁₅ O ₃ + H) ⁺ 1068.0 (M
210		14bd	3	5	92%	514.7 (M + 2H) ²⁺
211		14dg	1	3	90%	951.3 (M + H) ⁺
212		14dh	1	3	63%	934.4 (M + H) ⁺
213		14dj	1	3	83%	907.3 (M + H) ⁺
214		14di	1	3	83%	907.3 (M + H) ⁺
215		14ec	1	3	92%	502.7 (M + 2H) ²⁺
216		14ed	1	3	97%	1045 (M + H) ⁺
217		14ef	1	3	67%	512.5 (M + 2H) ²⁺
218		14eg	1	3	96%	512.1 (M + 2H) ²⁺
219		14eh	1	3	91%	519.5 (M + 2H) ²⁺
220		14ei	1	3	80%	470.0 (M + 2H) ²⁺ 938.9 (M + H) ⁺

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Table 2 continued

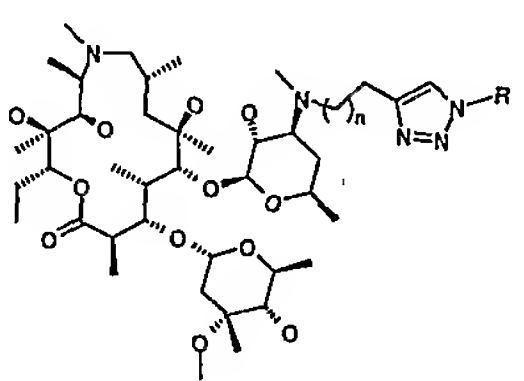
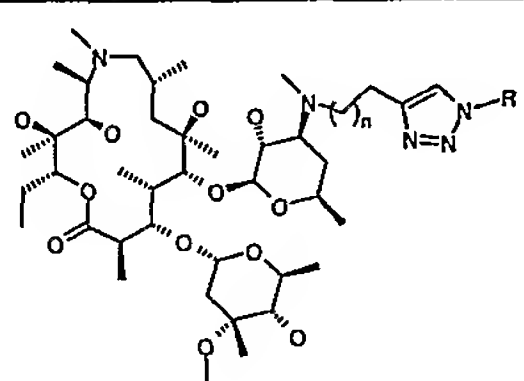
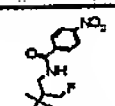
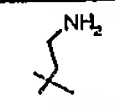
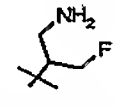
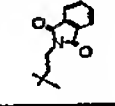
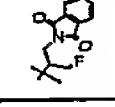
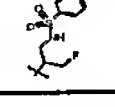
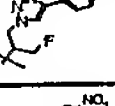
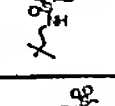
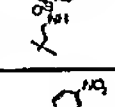
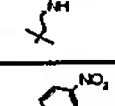
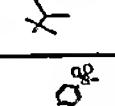
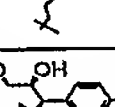
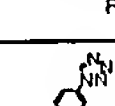
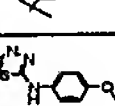
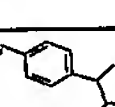
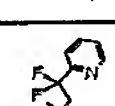
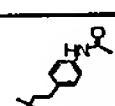
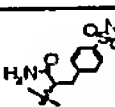

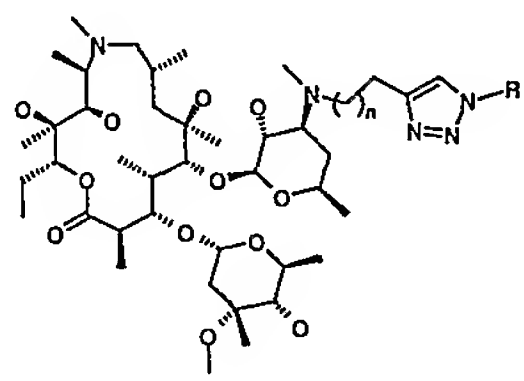
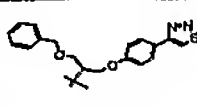
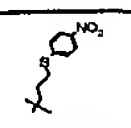
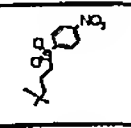
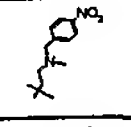
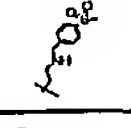
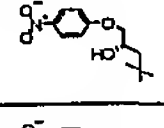
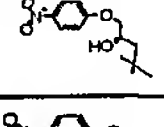
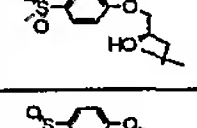
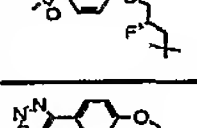
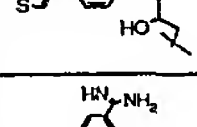
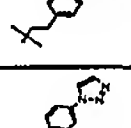
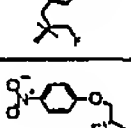
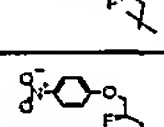
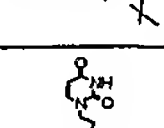
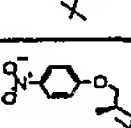
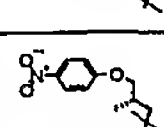
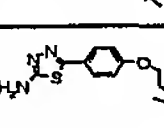
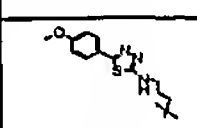
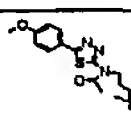

						
Compound	R	azide	n	Alkyne	Yield	LCMS (M/Z)
221		14ej	2	4	90%	511.6 (M + 2H) ²⁺
222		14el	1	3	76%	510.1 (M + 2H) ²⁺
223		14em	1	3	62%	1006.0 (M + H) ⁺
224		14en	1	3	47%	509.6 (M + 2H) ²⁺
225		14eo	1	3	69%	505.0 (M + 2H) ²⁺
226		N/A	1	3	97%	518.1 (M + 2H) ²⁺
227		14eq	1	3	73%	519.2 (M + 2H) ²⁺
228		14er	1	3	49%	531.1 (M + 2H) ²⁺
229		14es	1	3	89%	514.6 (M + 2H) ²⁺
230		14et	1	3	74%	505.6 (M + 2H) ²⁺
231		14eu	3	5	65%	519.8 (M + 2H) ²⁺
232		14ev	3	5	34%	505.6 (M + 2H) ²⁺
233		14ew	1	3	64%	515.6 (M + 2H) ²⁺ 1030.0 (M + H) ⁺
234		14ex	1	3	52%	516.6 (M + 2H) ²⁺ 1031.9 (M + H) ⁺
235		14ey	1	3	77%	530.6 (M + 2H) ²⁺
236		14ez	1	3	62%	525.1 (M + 2H) ²⁺
237		14fa	1	3	66%	556.6 (M + 2H) ²⁺
238		14fb	1	3	88%	408.8 (M + 3H) ³⁺
239		14w	3	5	44%	504.4 (M + 2H) ²⁺
240		14fd	1	3	83%	512.0 (M + 2H) ²⁺

Table 2 continued

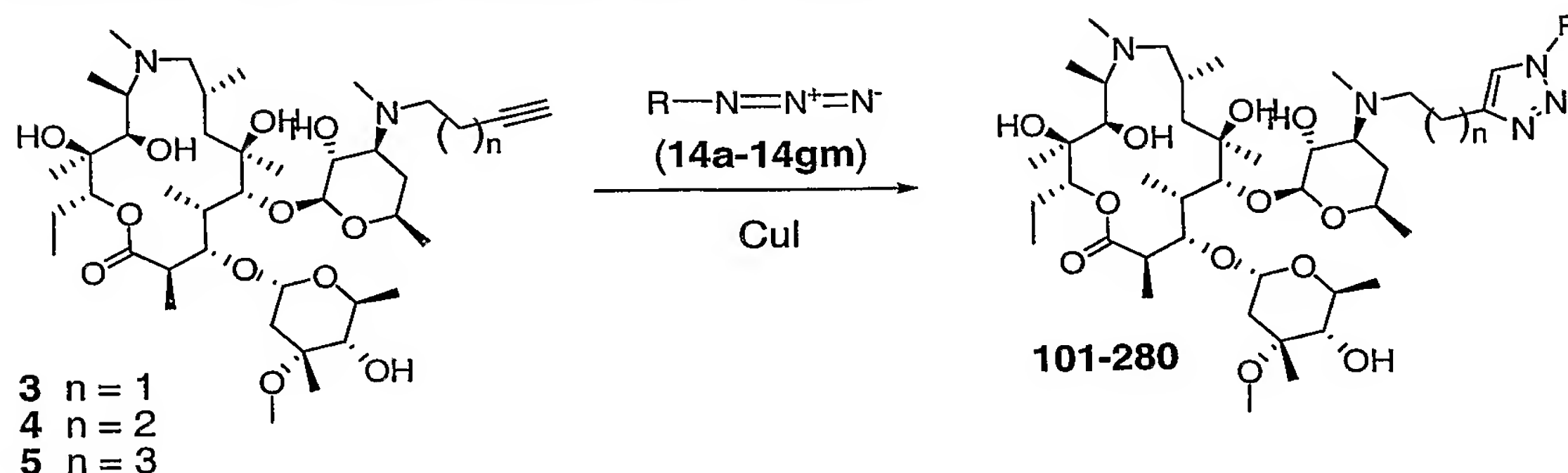
						
Compound	R	azide	n	Alkyne	Yield	LCMS (M/Z)
241		14fe	1	3	61%	528.1 (M + 2H) ²⁺
242		14ff	1	3	89%	437.5 (M + 2H) ²⁺
243		14fg	1	3	90%	453.3 (M + 2H) ²⁺
244		14fh	1	3	92%	502.6 (M + 2H) ²⁺ 1003.9 (M + H) ⁺
245		14fi	1	3	83%	518.5 (M + 2H) ²⁺
246		14fj	1	3	36%	546.1 (M + 2H) ²⁺
247		14fk	1	3	56%	540.1 (M + 2H) ²⁺
248		14fl	1	3	80%	530.1 (M + 2H) ²⁺
249		14fm	1	3	66%	546.6 (M + 2H) ²⁺
250		14fn	1	3	24%	505.0 (M + 2H) ²⁺
251		14fo	1	3	96%	497.6 (M + 2H) ²⁺ 993.7 (M + H) ⁺
252		14fp	1	3	95%	522.1 (M + 2H) ²⁺
254		14fr	1	3	30%	522.6 (M + 2H) ²⁺
255		14fs	1	3	29%	1003.7 (M + H) ⁺
256		14ft	1	3	27%	533.1 (M + 2H) ²⁺
257		14fu	1	3	89%	1002.8 (M + H) ⁺
258		14fv	1	3	91%	515.5 (M + 2H) ²⁺ 1029.8 (M + H) ⁺
259		14fw	1	3	20%	991.8 (M + H) ²⁺
260		14fx	1	3	50%	1056.8 (M + H) ⁺

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Table 2 continued

						
Compound	R	azide	n	Alkyne	Yield	LCMS (M/Z)
261		14fy	1	3	60%	578.1 (M + 2H) ²⁺ 1154.9 (M + H) ⁺
262		14fz	1	3	92%	533.1 (M + 2H) ²⁺
263		14ga	1	3	90%	529.5 (M + 2H) ²⁺
264		14gb	1	3	87%	511.9 (M + 2H) ²⁺
265		14gc	1	3	45%	521.5 (M + 2H) ²⁺
266		14gd	1	3	94%	513.6 (M + 2H) ²⁺
267		14ge	1	3	79%	513.6 (M + 2H) ²⁺
268		14gf	1	3	75%	530 (M + 2H) ²⁺
269		14gg	1	3	78%	531 (M + 2H) ²⁺ 1060.7 (M + H) ⁺
270		14gh	1	3	88%	533.1 (M + 2H) ²⁺ 1064.8 (M + H) ⁺
271		14gi	1	3	14%	976.7 (M + H) ⁺
272		14gj	1	3	76%	530 (M + 2H) ²⁺
273		14gk	1	3	56%	514.6 (M + 2H) ²⁺ 1064.8 (M + H) ⁺
274		14gl	1	3	61%	514.6 (M + 2H) ²⁺ 1064.8 (M + H) ⁺
275		14gm	1	3	55%	485.1 (M + 2H) ²⁺
276		14gn	1	3	85%	512.6 (M + 2H) ²⁺ 1024 (M + H) ⁺
277		14go	1	3	88%	512.6 (M + 2H) ²⁺ 1024 (M + H) ⁺
278		14fq	1	3	46%	532.4 (M + 2H) ²⁺
279		14ab	1	3	23%	539.5 (M + 2H) ²⁺
280		14ac	1	3	42%	560.6 (M + 2H) ²⁺

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Scheme 101: Synthesis of compounds of Table 2

Triazoles **101 -280** were produced from alkynes **3**, **4**, and **5** using azides **14a-14gm** under one of several similar reaction conditions as exemplified by Conditions A, B, C, and D below for compounds **151**, **155**, **159**, and **158** respectively. Use of Conditions A and C, which do not include the step of degassing the reaction mixture, resulted in the formation of significant amounts of iodinated side-products in addition to the desired product and thereby generally produced lower isolated yields. Additionally, reduction of the amount of copper iodide used in the reaction to 0.5 molar equivalents or less as in conditions B and D also resulted in reduced formation of iodinated by-products. As demonstrated in Condition D, the presence of Hunig's base was not essential for the success of the triazole formation step; however, it was found preferable that the base be included since it often resulted in a higher rate of reaction and allowed correspondingly shorter reaction times to be used.

Condition A:**Synthesis of triazole 151**

To a stirred solution of alkyne **3** (30 mg, 0.04 mmol), azide **14az** (10 mg, 0.07 mmol) and Hunig's base (10 μ L) in 0.5 mL tetrahydrofuran (THF) was added CuI (5 mg, 0.03 mmol). The mixture was stirred at ambient temperature for 16h then diluted with CH_2Cl_2 (10 mL) and washed with a 3:1 mixture of saturated aqueous NH_4Cl and 28% aqueous NH_4OH (10 mL) and with brine (10 mL) the aqueous washes were back-extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over K_2CO_3 , filtered, and concentrated to afford 52 mg of crude product which was purified by chromatography on silica gel (elution with 40:1 2M NH_3 in MeOH and CH_2Cl_2) to give the title compound as a white solid (22 mg, 63%). (943.4 $[\text{M} + \text{Na}]^+$, 921.3 $[\text{M} + \text{H}]^+$, 461.3 $[\text{M} + 2\text{H}]^{2+}$.

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Condition B:**Synthesis of triazole 155**

A solution of alkyne **3** (80 mg, 0.10 mmol) and azide **14bd** (21 mg, 0.12 mmol) and Hunig's base in 0.4 mL THF was thoroughly degassed by alternately evacuating the reaction vessel and purging with dry argon. CuI was then added (2 mg, 0.01 mmol) and the mixture was further degassed. The mixture was stirred under argon for 6h then diluted with CH₂Cl₂ (20 mL) and washed with a 3:1 mixture of saturated aqueous NH₄Cl and 28% aqueous NH₄OH (10 mL) and with brine (10 mL) the aqueous washes were back-extracted with CH₂Cl₂ (2 x 15 mL). The combined organic extracts were dried over K₂CO₃, filtered, and concentrated to afford 115 mg of crude product which was purified by chromatography on silica gel (eluted with 2M NH₃ in MeOH (2.5%) and CH₂Cl₂ (97.5%)). To give the title compound as a white solid (94 mg, 0.094 mmol). MS (ESI) *m/e* 999.3 [M + H]⁺, 500.4 [M + 2H]²⁺.

Condition C:**Synthesis of triazole 159**

To a stirred solution of alkyne **3** (79 mg, 0.10 mmol) and Hunig's base (0.2 mL) in 3 mL THF was added azide **14bh** (115 mg, 0.50 mmol) and CuI (20 mg, 0.10 mmol). The reaction mixture was stirred under argon for 60h then poured into saturated aqueous NH₄Cl and extracted with CH₂Cl₂. The organic extracts were dried over Na₂SO₄, filtered, and concentrated to afford a crude residue which was purified by silica gel chromatography (eluted with 25:1:0.1 CH₂Cl₂:MeOH:NH₄OH) and then by preparative TLC (elution with 25:1:0.1 CH₂Cl₂:MeOH:NH₄OH) to afford the title compound as a white solid (38 mg, 0.037 mmol). MS (ESI) *m/e* 1017.9 [M + H]⁺, 509.7 [M + 2H]²⁺.

Condition D**Synthesis of triazole 158.**

A solution of alkyne **3** (120 mg, 0.15 mmol) and azide **14bg** (60 mg, 0.25 mmol) in 2.7 mL THF was thoroughly degassed by alternately evacuating the reaction vessel and purging with dry argon. CuI was then added (10 mg, 0.05 mmol) and the mixture was further degassed. The mixture was stirred under argon for 4h then concentrated in vacuo, dissolved in CH₂Cl₂ (1 mL), and placed directly on a silica gel column. Elution with 2 molar (M) NH₃ in MeOH (3%) and

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CH₂Cl₂ (97%) gave the title compound as a white solid (80 mg, 0.08 mmol). MS (ESI) *m/e* 1019.6[M + H]⁺, 510.6 [M + 2H]²⁺.

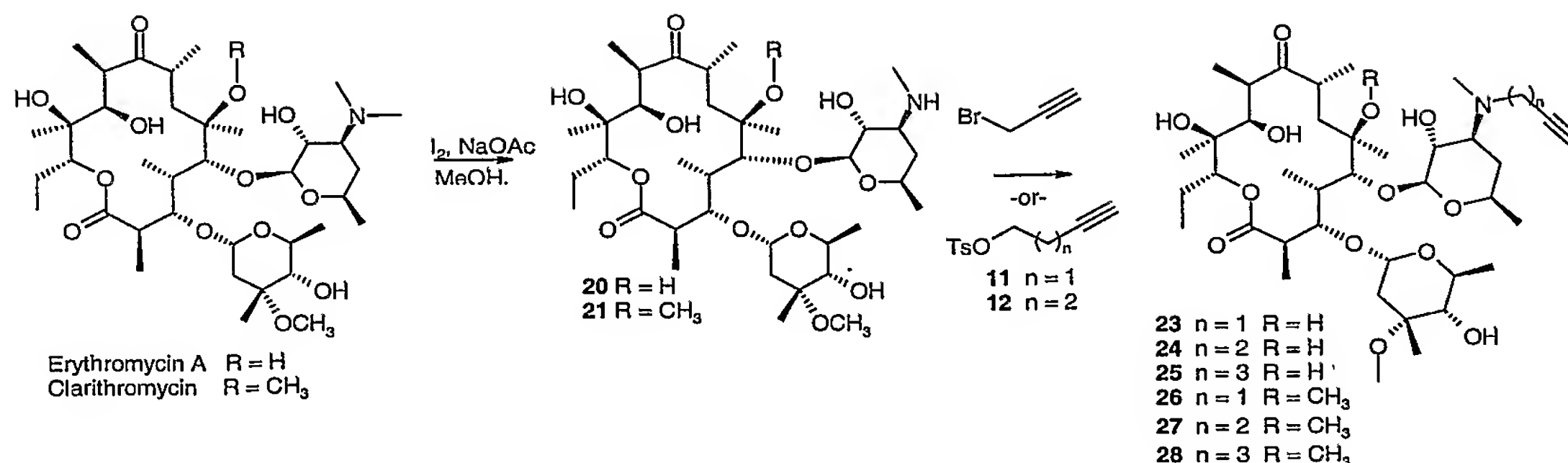
The remainder of the compounds in Table 2 were synthesized from alkynes **3**, **4**, or **5** and the appropriate azides **14a-14gm** as indicated in table 2 using conditions closely analogous to one of the four procedures above. The time required for each reaction to proceed to completion was variable and was dependent upon several factors including: the specific substrates; the amount of Cu(I) salt used; the presence or absence of Hunig's base; and the concentration of the reactants. Reactions were monitored for the disappearance of the starting materials by TLC and/or LCMS and were typically allowed to run for between about 2h to about 72h. Reactions were stopped when analysis demonstrated that the starting alkyne substrate had been substantially consumed. The workup and purification protocols exemplified in conditions A – D are typical of those used for all reactions. Slight modifications to the described workup procedures may have been used (such modifications include the use of different aqueous wash solutions, different organic solvents for extraction, the use of other anhydrous salts for the drying of organic extracts, and the employment of different solvent mixtures for the chromatographic purification of the compounds). In all cases, the methods used for the workup of the reaction mixtures, the extraction of products, the drying of organic extracts, and for the isolation and purification of the title compounds were typical of procedures familiar to those trained in the art of organic synthesis. There were no specific or unusual protocols employed in the isolation and purification of the reaction products that were found to be critical in these processes. The isolated chemical yields for the synthesis of compounds **101-280** were variable and are indicated in the penultimate column of Table 2.

Example 2 - Synthesis of Compounds 301-357

Schemes 103 and 104 below depict the synthesis of compounds **301-357**. Demethylation of erythromycin A selectively produced 3'-N-desmethyl-erythromycin A **20**. Similarly, demethylation of clarithromycin yielded 3'-N-desmethyl-clarithromycin **21**. Amines **20** and **21** were selectively N-alkylated with propargyl bromide or with tosylates **11** or **12** to produce alkynes **23**, **24**, **25**, **26**, **27**, or **28**. As shown in Scheme 2 alkynes **23-28** are reacted with azides **14a-14eb** in the presence of copper (I) iodide to selectively afford the triazoles **301-357**.

Scheme 103: Synthesis of alkynes 23-28.

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Synthesis of 3'-N-desmethyl-erythromycin A 20

Compound **20** was made from erythromycin A employing the procedure described in U.S. Patent No. 3,725,385.

Synthesis of 3'-N-desmethyl-clarithromycin 21

To a mixture of clarithromycin (1.00 g, 1.3 mmol) and NaOAc \cdot 3H₂O (0.885 g, 6.5 mmol) was added MeOH-H₂O (20 mL, 4:1), and the mixture heated to 55-60°C. Iodine (0.330 g, 1.3 mmol) was added portion-wise and the reaction stirred at 55-60°C for 3 h. The reaction mixture was poured into 50 mL chloroform (CHCl₃) containing 1 mL ammonium hydroxide. It was extracted with CHCl₃ (4 x 50 mL), washed with water (70 mL) containing 5 mL ammonium hydroxide, dried (anhydrous Na₂SO₄), concentrated, and purified by flash chromatography (silica gel, CHCl₃:MeOH:NH₄OH 100:10:0.1) to afford **21**. Yield: 0.9g (92%).

Synthesis of alkyne 24

A mixture of 3'-N-desmethyl-erythromycin A **20** (1.0 g, 1.4 mmol) and tosylate **11** (1.25 g, 5.6 mmol) in anhydrous THF (15 mL) and Hunig's base (2.2 mL, 11.9 mmol) was kept stirring at 55°C for 48 hours. The reaction was poured into CH₂Cl₂ (50 mL), extracted with 2% aqueous NH₄OH (3 x 30 mL) and saturated brine (1 x 30 mL). The organic layer was dried over Na₂SO₄ and the solvent was evaporated away. The crude was purified on a silica gel column eluting with CH₂Cl₂/MeOH 10:1 to give **24** (0.35 g, 32%).

Synthesis of alkyne 23

Alkyne **23** was made from 3'-N-desmethyl-erythromycin A **20** and propargyl bromide using the same procedure described for the synthesis of compound **24**.

Synthesis of alkyne 25

Alkyne **25** was made from 3'-*N*-desmethyl-erythromycin A **20** and tosylate **12** using the same procedure described for the synthesis of compound **24**.

Synthesis of alkyne 26

- 5 Alkyne **26** was made from 3'-*N*-desmethyl-clarithromycin **21** and propargyl bromide using the same procedure described for the synthesis of compound **24**.

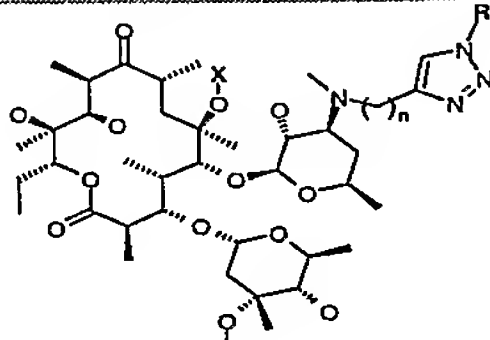
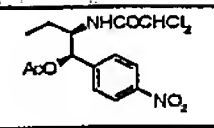
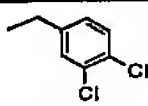
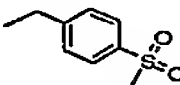
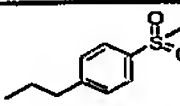
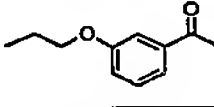
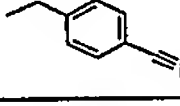
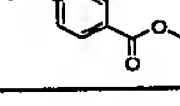
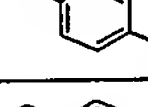
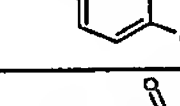
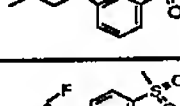
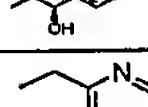
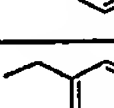
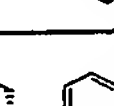
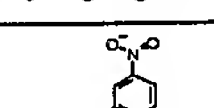

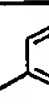
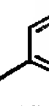

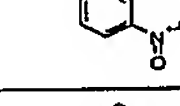
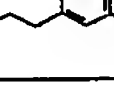

Synthesis of alkyne 27

Alkyne **27** was made from 3'-*N*-desmethyl-clarithromycin **21** and tosylate **11** using the same procedure described for the synthesis of compound **24**.

10 **Synthesis of alkyne 28**

Alkyne **28** was made from 3'-*N*-desmethyl-clarithromycin **21** and tosylate **12** using the same procedure described for the synthesis of compound **24**.

Table 3

							
Compound	R	n	X	Azide	Alkyne	Yield	LCMS (M/Z)
301		3	H	14cy	8	77%	1175.3 (M+H) ⁺
302		2	CH ₃	14da	9	30%	987.8 (M+H) ⁺ 1009.8 (M+Na) ⁺
303		2	CH ₃	14c	9	21%	997.8 (M+H) ⁺ 1009.8 (M+Na) ⁺
304		2	CH ₃	14b	9	57%	1011.8 (M+H) ⁺ 1033.8 (M+Na) ⁺
305		2	CH ₃	14u	9	82%	991.5 (M+H) ⁺
306		2	CH ₃	14db	9	68%	945.5 (M+H) ⁺ 966.3 (M+Na) ⁺
307		2	CH ₃	14dc	9	83%	978.4 (M+H) ⁺ 999.3 (M+Na) ⁺
308		2	CH ₃	14dd	9	77%	997.2 (M+H) ⁺ 1021.6 (M+Na) ⁺
309		2	CH ₃	14de	9	92%	953.4 (M+H) ⁺ 975.4 (M+Na) ⁺
310		2	CH ₃	14df	9	92%	1028.3 (M+H) ⁺ 1049.2 (M+Na) ⁺
311		2	CH ₃	14au	9	59%	1059.9 (M+H) ⁺ 1081.8 (M+Na) ⁺
312		2	CH ₃	14az	9	66%	921.2 (M+H) ⁺ 943.3 (M+Na) ⁺
313		2	CH ₃	14ba	9	80%	921.1 (M+H) ⁺ 943.3 (M+Na) ⁺
314		2	CH ₃	14bq	9	79%	1008.9 (M+H) ⁺ 1030.9 (M+Na) ⁺
315		2	CH ₃	14dg	9	95%	951.4 (M+H) ⁺
316		2	CH ₃	14dh	9	88%	933.5 (M+H) ⁺
317		2	CH ₃	14di	9	66%	906.7 (M+H) ⁺
318		2	CH ₃	14dj	9	90%	906.6 (M+H) ⁺
319		2	CH ₃	14w	9	91%	979.3 (M+H) ⁺
320		2	CH ₃	14v	9	93%	964.4 (M+H) ⁺
321		2	CH ₃	14dk	9	91%	979.2 (M+H) ⁺

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Table 3 continued

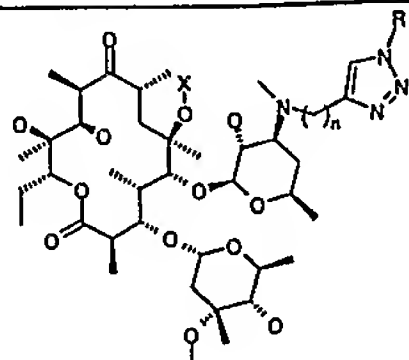
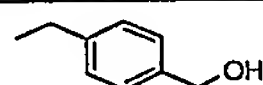
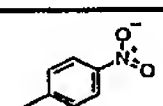
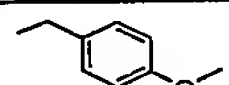
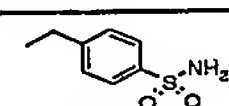
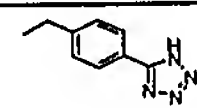
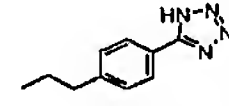
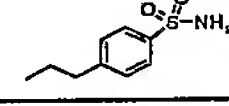
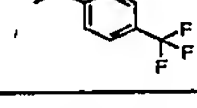
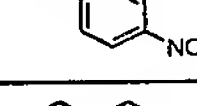
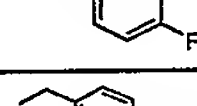
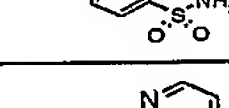
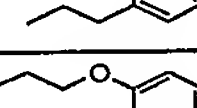

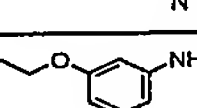
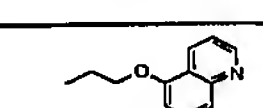
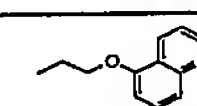
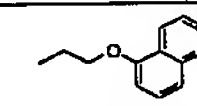
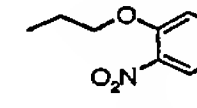
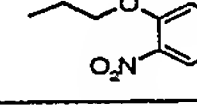
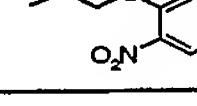

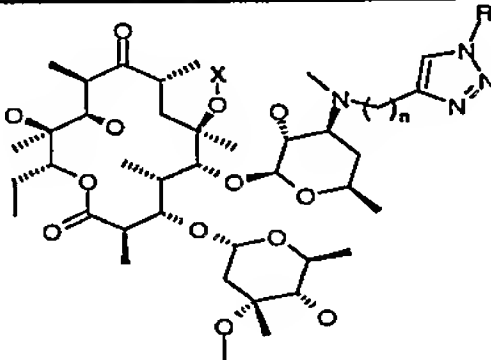
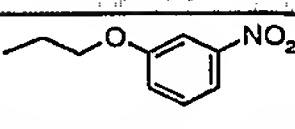
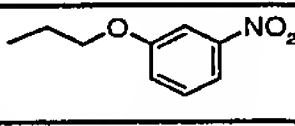
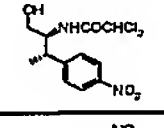
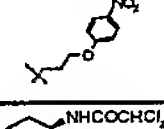
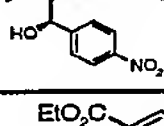
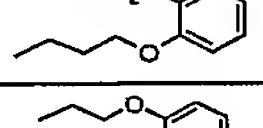
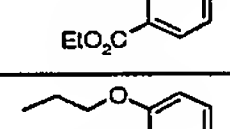
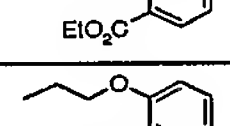
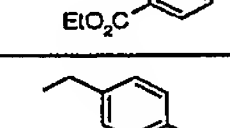
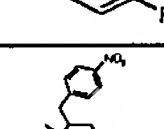
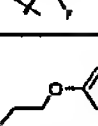
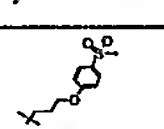
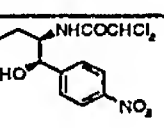
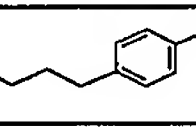
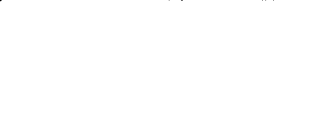
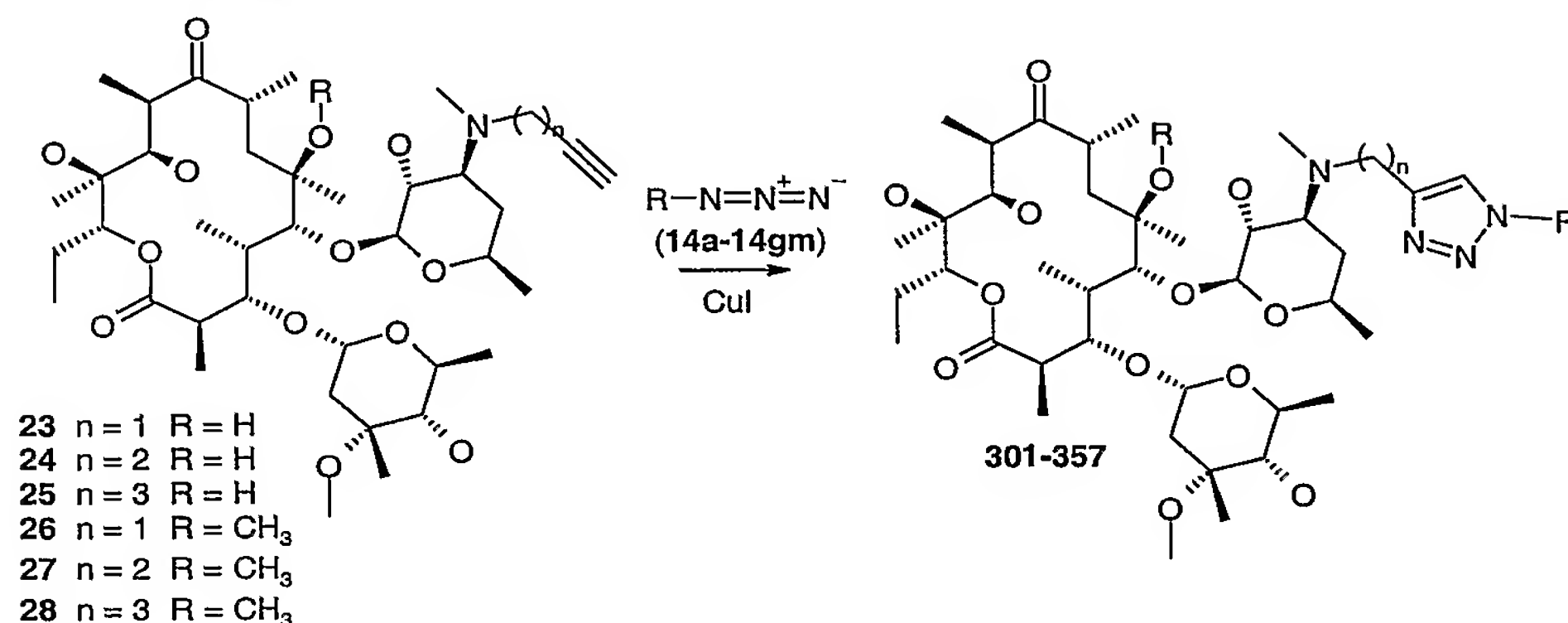
							
Compound	R	n	X	Azide	Alkyne	Yield	LCMS (M/Z) ⁺
322		2	CH ₃	14dm	9	89%	949.4 (M+H) ⁺
323		2	CH ₃	14dn	9	92%	950.4 (M+H) ⁺
324		2	CH ₃	14do	9	84%	950.2 (M+H) ⁺
325		2	CH ₃	14bd	9	84%	999.3 (M+H) ⁺
326		2	CH ₃	14x	9	68%	987.3 (M+H) ⁺
327		2	CH ₃	14dp	9	66%	1001.3 (M+H) ⁺
328		2	CH ₃	14be	9	68%	1012.2 (M+H) ⁺
329		2	CH ₃	14dq	9	84%	987.3 (M+H) ⁺
330		3	CH ₃	14v	10	94%	978.43 (M+H) ⁺
331		3	CH ₃	14dr	10	86%	951.2 (M+H) ⁺
332		3	CH ₃	14bd	10	86%	1012.3 (M+H) ⁺
333		2	CH ₃	14dx	9	73%	935 (M+H) ⁺
334		2	CH ₃	14t	9	57%	968 (M+H) ⁺
335		2	CH ₃	14dy	9	38%	949 (M+H) ⁺
336		2	CH ₃	14dz	9	52%	1007 (M+H) ⁺
337		3	H	14aw	8	78%	1001.4 (M+H) ⁺
338		2	H	14aw	7	81%	1001.4 (M+H) ⁺
339		1	H	14aw	6	81%	1001.4 (M+H) ⁺
340		1	H	14ds	6	63%	967 (M+H) ⁺
341		2	H	14ds	7	78%	981 (M+H) ⁺
342		3	H	14ds	8	63%	995 (M+H) ⁺

Table 3 continued

							
Compound	R	n	X	Azide	Alkyne	yield	LCMS (M/Z)
343		2	H	14a	7	34%	981 (M+H) ⁺
344		3	H	14a	8	67%	995 (M+H) ⁺
345		3	H	14dt	8	75%	1133.3 (M+H) ⁺
346		2	CH ₃	14et	9	89%	1008.9 (M+H) ⁺
347		3	H	14du	8	84%	1133.3 (M+H) ⁺
348		2	H	14dv	7	68%	1022 (M+H) ⁺
349		1	H	14dw	6	69%	994 (M+H) ⁺
350		2	H	14dw	7	35%	1008 (M+H) ⁺
351		3	H	14dw	8	30%	1022 (M+H) ⁺
352		2	CH ₃	14dr	9	97%	937.3 (M+H) ⁺
353		2	CH ₃	14bt	9	85%	1010.8 (M+H) ⁺ 1032.8 (M+Na) ⁺
354		1	H	14a	6	95%	967 (M+H) ⁺
355		2	CH ₃	14fp	9	95%	1041.8 (M+H) ⁺ 1063.7 (M+Na) ⁺
356		2	H	14du	8	73%	1122.4 (M+H) ⁺
357		2	CH ₃	14ej	9	89%	1006.9 (M+H) ⁺ 1028.9 (M+Na) ⁺

Scheme 104: Synthesis of compounds of Table 3

Triazoles **301 -357** were produced from alkynes **23-28** using azides **14a-14gm** under reaction conditions as exemplified by Conditions A, B, C, and D above for compounds **101-280** in Example 1. As above, the use of Conditions A and C, which do not include the step of degassing the reaction mixture, resulted in the formation of iodinated side-products and generally lower yields. Additionally, reduction of the amount of copper salt used in the reaction to 0.5 molar equivalents or less as in conditions B and D resulted in reduced formation of iodinated by-products.

The compounds in Table 2 were synthesized using conditions closely analogous to conditions A, B, C, and D described above. The time required for each reaction to proceed to completion was again variable and was dependent upon the several variables noted above including: the specific substrates, the amount of Copper (I) salt used, the presence or absence of Hunig's base, and the concentration of the reactants. Reactions were monitored for the disappearance of the starting materials by TLC and/or LCMS and were typically allowed to run for between about 2h to about 72h with the majority being about 16h. Reactions were stopped when analysis demonstrated that the starting alkyne substrate had been substantially consumed. The workup and purification protocols exemplified in conditions A-D are typical of those used for all products in Table 2. Slight modifications to the described workup procedures may have been used as set forth above for the compounds of Table 2.

Example 3 - Synthesis of Compounds 401-417

Compounds **401-417** shown in Table 4 were derived from telithromycin using methodology analogous to that described above for the compounds of Tables 2 and 3. Telithromycin was selectively *N*-demethylated and then alkylated with tosylate **11** as described

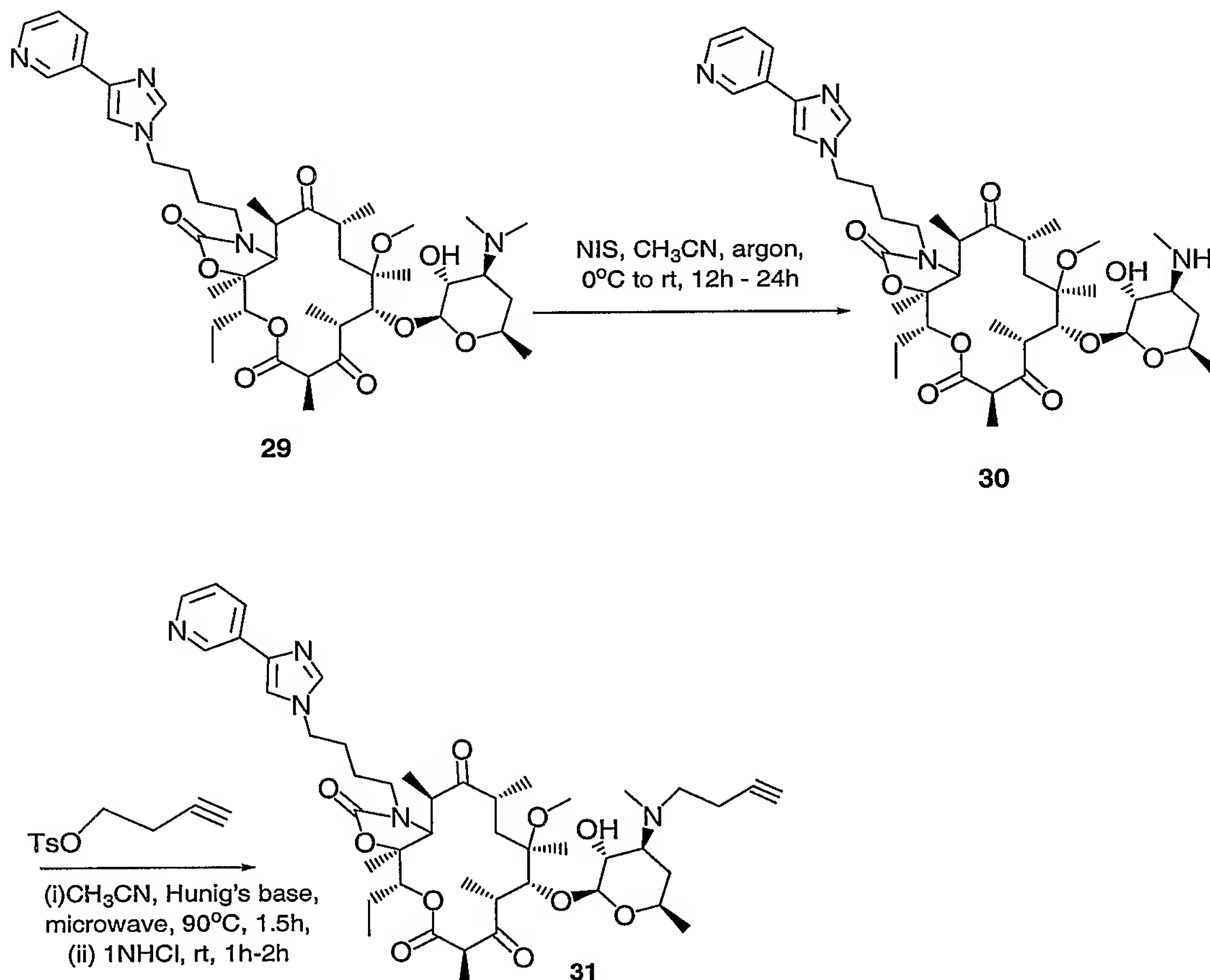
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for azithromycin, erythromycin and clarithromycin above. The resulting alkyne was elaborated to the corresponding triazoles using the same copper catalyzed [3 + 2] cycloaddition reaction with azides **14** discussed above.

Synthesis of 3'-N-Desmethyl telithromycin **30**

- 5 To a solution of telithromycin **29** (3.0 g, 3.60 mmol) in anhydrous acetonitrile (70 mL) was added N-iodosuccinimide (NIS) (0.98 g, 4.32 mmol) in two portions within 30 min at 0°C under argon atmosphere. The mixture was allowed to warm to rt and stirred overnight. CH₂Cl₂ (250 mL) and 5 % Na₂S₂O₃ (80 mL) were added and the two layers separated. The organic layer was extracted with 5 % Na₂S₂O₃ (1 X 80 mL), dilute NH₄Cl (1 X 80 mL) and dried over Na₂SO₄.
- 10 Solvent was evaporated and the crude was purified on silica gel eluting with 0 – 8 % methanolic ammonia (2N NH₃) in CH₂Cl₂ to give compound **30** as white solid (1.95 g, 68 %). MS (ESI) M/E; M+H⁺ 798.6.

Scheme 105 Synthesis of alkyne **31**.



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Synthesis of 3'-N-(but-3-ynyl) telithromycin 31

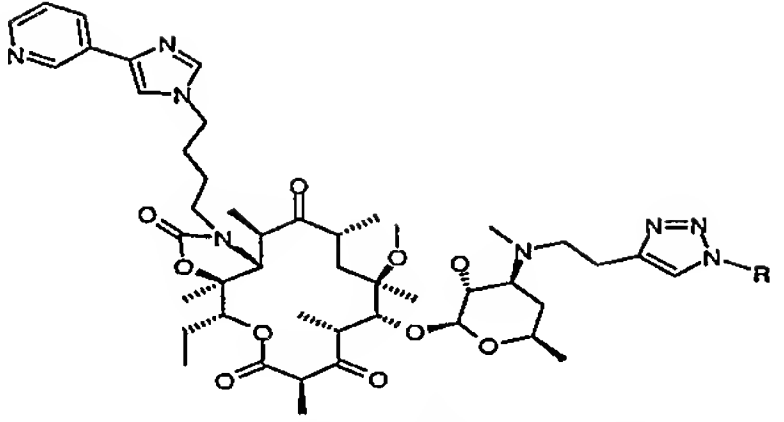
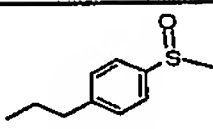
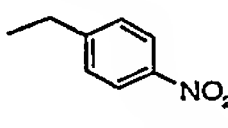
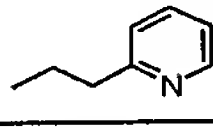
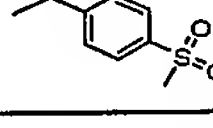
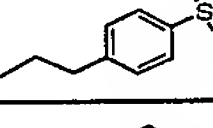
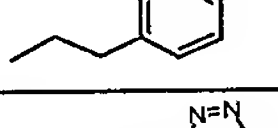
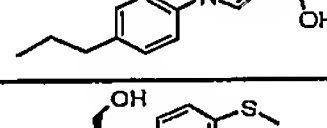
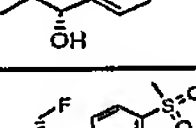
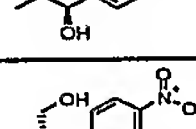
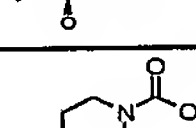
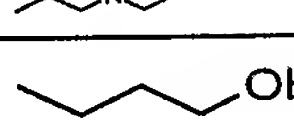
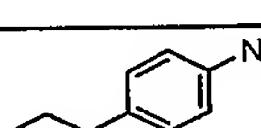
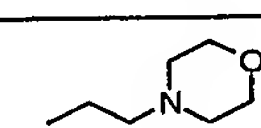
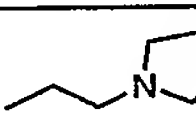
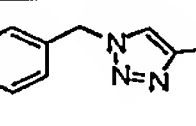
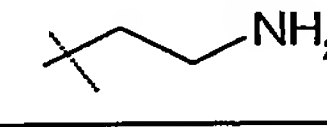

Protocol A: A mixture of amine **30** (0.66 g, 0.83 mmol) and tosylate **11** (0.33 g, 1.49 mmol) in THF (15 mL) and Hunig's base (3 mL) was heated at 90°C for 5 days. The solvent was
5 evaporated; the residue was dissolved in 1N HCl (50 mL) and kept stirring at room temperature for about 1h. CH₂Cl₂ (30 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 X 30 mL) and basified with NaOH (1N) to form a whitish-suspension. The suspension was extracted with CH₂Cl₂ (3 X 30 mL) and the organic layer was dried over Na₂SO₄. Solvent was evaporated and the crude was purified on silica gel eluting with
10 0 – 6 % methanolic ammonia (2N NH₃) in CH₂Cl₂ to give compound **31** as white solid (0.12 g, 17 %). MS (ESI) *m/e* 850.8 (M+H)⁺.

Synthesis of 3'-N-(but-3-ynyl) telithromycin 31

Protocol B: A mixture of amine **30** (0.66 g, 0.83 mmol), and tosylate **11** (0.40 g, 1.84 mmol) in
15 acetonitrile (10 mL) and Hunig's base (0.18 mL, 1.0 mmol) was microwave heated to 90°C within 10 min and maintained at 90°C for 1.5h. The reaction was vented within 15 min and solvent was evaporated. The residue was dissolved in 1N HCl (60 mL) and kept stirring at room temperature for about 2h. CH₂Cl₂ (30 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 X 30 mL) and basified with 50 % KOH to form a
20 whitish-suspension. The suspension was extracted with CH₂Cl₂ (3 X 30 mL) and the organic layer was dried over Na₂SO₄. The solvent was evaporated and the crude was purified by preparative TLC (2000 micron plate) eluting with CH₂Cl₂/methanolic ammonia (2N NH₃) 12:1 to give compound **31** as white solid (0.19 g, 27 %). MS (ESI) *m/e* 850.8 (M+H)⁺.

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Table 4

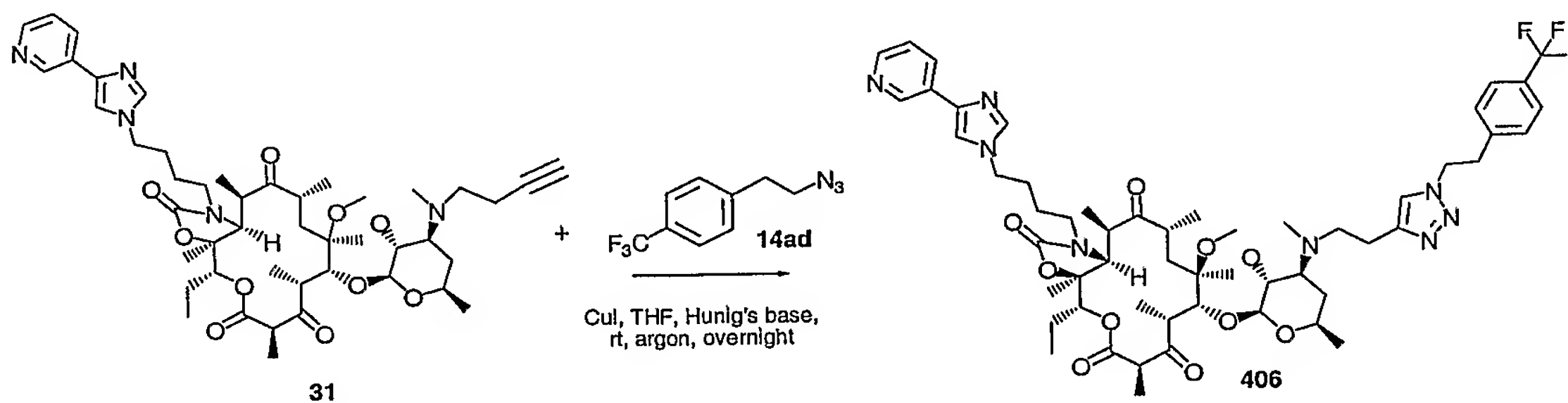
				
Compound	R	Azide	Yield	LCMS M/Z
401		14cf	99%	538.7 (M + 2H) ²⁺
402		14v	67%	515.1 (M + 2H) ²⁺
403		14dx	97%	500.1 (M + 2H) ²⁺
404		14b	83%	531.7 (M + 2H) ²⁺
405		14db	81%	530.7 (M + 2H) ²⁺ 1059.9 (M + H) ⁺
406		14ad	34%	533.7 (M + 2H) ²⁺
407		14aa	51%	548.5 (M + 2H) ²⁺ 1116.9 (M + Na) ⁺
408		14ag	68%	548.2 (M + 2H) ²⁺
409		14au	66%	545.8 (M + 2H) ²⁺
410		14s	38%	562.8 (M + 2H) ²⁺
411		14ea	61%	545.1 (M + 2H) ²⁺
412		14eb	98%	553.7 (M + 2H) ²⁺ 1127.9 (M + Na) ⁺
413		14w	52%	476.6 (M + 2H) ²⁺ 973.9 (M + Na) ⁺
414		14by	78%	522.1 (M + 2H) ²⁺
415		14j	86%	504.1 (M + 2H) ²⁺ 1029.1 (M + Na) ⁺
416		14z	89%	496.1 (M + 2H) ²⁺ 991.1 (M + H) ⁺
417		14ff	30%	469.0 (M + 2H) ²⁺ 958.9 (M + Na) ⁺

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Triazoles **401 -417** were produced from alkyne **31** using azides **14a-14gm** under reaction conditions similar to those described above for the compounds of Tables 4 and 5. As above, the use of conditions which did not include the step of degassing the reaction mixture, resulted in the formation of iodinated side-products and generally lower yields. Additionally, reduction of the amount of copper salt used in the reaction to 0.5 molar equivalents or less resulted in reduced formation of iodinated by-products.

The procedure detailed below for the synthesis of compound **406** from azide **14ad** is typical of those used for all compounds in Table 4. As described in Example 1, the time required for each reaction to proceed to completion was again variable and was dependent upon the several variables noted above including: the specific substrates, the amount of Copper (I) salt used, the presence or absence of Hunig's base, and the concentration of the reactants. Reactions were monitored for the disappearance of the starting materials by TLC and/or LCMS and were typically allowed to run for between about 6h to about 24h and were stopped when analysis demonstrated that the starting alkyne substrate had been substantially consumed. The workup and purification protocols exemplified in conditions A-D in Example 1 are typical of those used for all products in Table 6. Slight modifications to the described workup procedures may have been used as described above in Example 1 for the synthesis of compounds of Table 4.

Scheme 106: Synthesis of compound **406**



Synthesis of compound **406**

This compound was obtained from the reaction of alkyne **31** (0.06 g, 0.07 mmol) with azide **14ad** (0.030 g, 0.14 mmol) under argon atmosphere in the presence of CuI (0.030 g, 0.14 mmol) in THF (5 mL) and Hunig's base (0.05 mL) mixture at room temperature overnight with workup as described before. The crude reaction was purified by preparative TLC (2000 micron

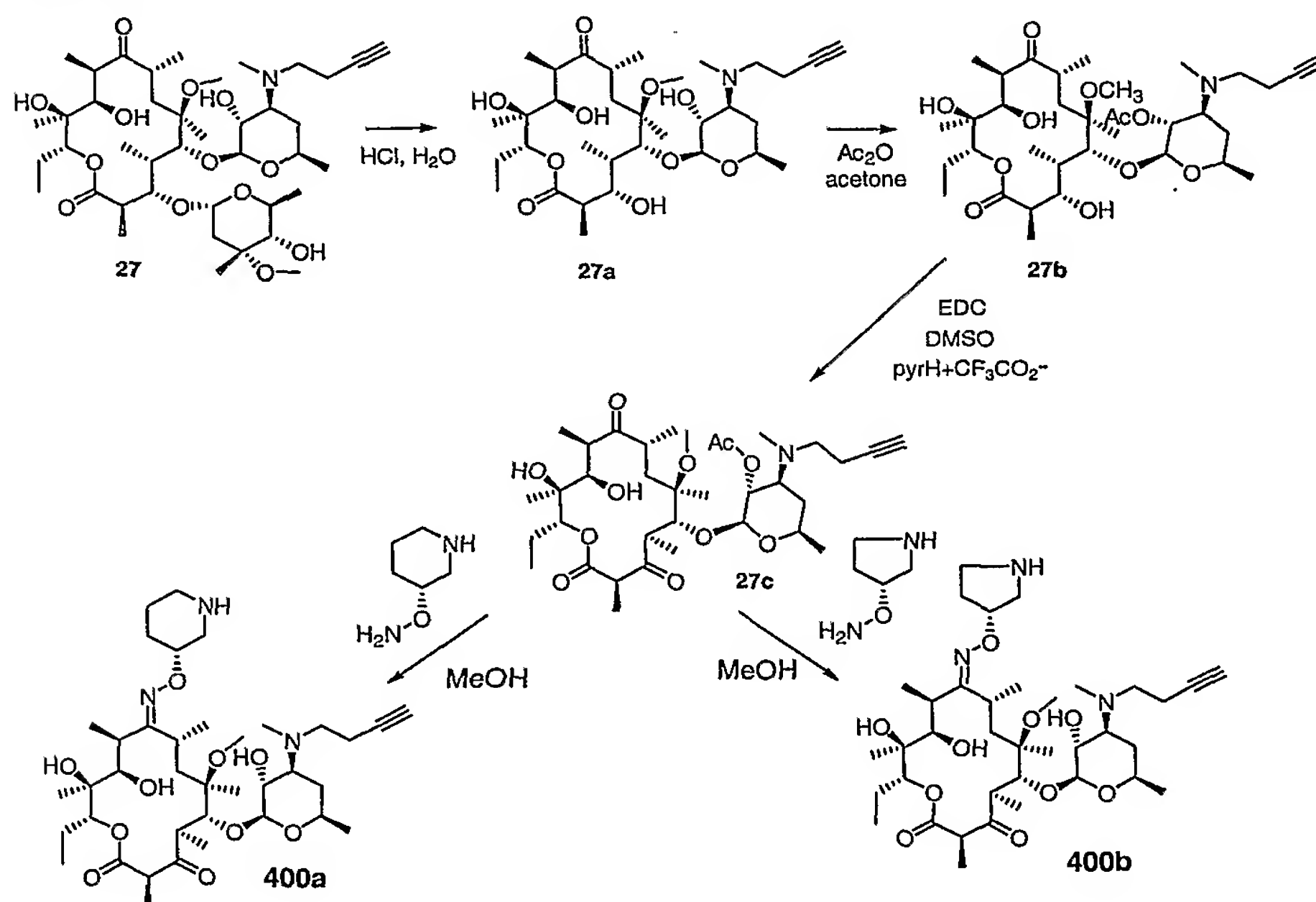
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plate) eluting with CH₂Cl₂/MeOH 12:1 to give triazole **406** as white solid (0.025g, 34 %). MS (ESI) *m/e* 533.7 (M+2H)²⁺.

Example 4: Synthesis of compounds 425-451

The oximes **425-433** of Table 5 were synthesized from alkynes **400a** to **400i** by copper(I)-promoted cycloaddition with azides **14a-14gm** in a manner analogous to the procedures presented previously. Alkyne precursors **401a – 401i** with substituted oxime functionality at the 9-position of the macrocyclic ring were prepared from alkynes **27**, **24**, and as shown below.

10 Scheme 107



Synthesis of alcohol 27a

To the alkyne **27** (0.700 g) was added 10 mL 0.9N HCl and the mixture was stirred for 4 h at room temperature. The reaction mixture was saturated with sodium chloride and was adjusted to pH 8 using aqueous NH₄OH solution. The solution was extracted with ethyl acetate (3 x 30 mL), dried (with Na₂SO₄), and concentrated under reduced pressure. Purification of the crude reaction mixture by flash chromatography (silica gel, 60% ethyl acetate in hexane) afforded 0.200 g (35% yield) of the descladinose derivative **27a**. Data for **27a**: ¹HNMR (300

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MHz, CDCl₃, partial): δ 0.82 (t, 3H), 2.25 (s, 3H), 3.00 (s, 3H), 3.25 (dd, 1H), 3.55 (m, 2H), 3.70 (s, 1H), 3.85 (s, 1H), 3.95 (s, 1H), 4.40 (d, 1H), 5.15 (dd, 1H).

Synthesis of acetate 27b

To a solution of **27a** (0.200 g, 0.32 mmol) in acetone (2 mL) was added acetic anhydride (0.050 mL, 0.5 mmol) and the mixture was stirred overnight at room temperature. The reaction was quenched with water and extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with saturated sodium bicarbonate (3 x 50 mL), dried (anhydrous Na₂SO₄), and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (silica gel, 50% ethyl acetate in hexane) to yield 0.100 g (50% yield) of acetate **27b**. Data for **27b**: ¹HNMR(300 MHz, CDCl₃, partial): δ 0.84 (t, 3H), 2.00 (s, 3H), 2.20 (s, 3H), 2.90 (s, 3H), 3.00 (q, 1H), 3.25 (s, 1H), 3.47 (m, 2H), 3.70 (bs, 1H), 3.82 (bs, 1H), 3.97 (s, 1H), 4.60 (d, 1H), 4.77 (dd, 1H), 5.15 (dd, 1H).

Synthesis of ketolide 27c

To a solution of acetate **27b** (0.090 g, 0.134 mmol), EDC•HCl (0.172 g, 0.90 mmol), and dimethyl sulfoxide (DMSO) (0.171 mL, 2.41 mmol) in CH₂Cl₂ (1.5 mL) was added dropwise a solution of pyridinium trifluoroacetate (0.174 g, 0.90 mmol) in CH₂Cl₂ (1 mL) at 15⁰C. The reaction mixture was slowly warmed up to room temperature and stirred for 3 h. The reaction was quenched with water (2 mL), and allowed to stir for 30 min. The mixture was then poured into CHCl₃ (50 mL), and the organic layer was washed with water (2 x 50 mL), dried (over anhydrous Na₂SO₄), and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, 30% ethyl acetate in hexane) to yield 0.070g (78%) of the ketolide **27c**. Data for **27c**: MS (ESI) *m/e* 668 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 0.86 (t, 3H), 2.00 (s, 3H), 2.24 (s, 3H), 2.70 (s, 3H), 2.95-3.10 (m, 1H), 3.15-3.05 (m, 1H), 3.45-3.65 (m, 1H), 3.80 (q, 1H), 3.90 (s, 1H), 4.28 (d, 1H), 4.40 (d, 1H), 4.76 (dd, 1H), 5.10 (dd, 1H).

Synthesis of oxime 400a

To a solution of **27c** (2.0 g, 2.9 mmol) in MeOH (10 mL) was added (R)-N-Piperidin-3-yl-hydroxylamine hydrobromide (1.26 g, 4.4 mmol). The reaction mixture was stirred at rt for 14h. The mixture was then poured into (50 mL) and water (50 mL) the pH was adjusted to 11 by addition of NH₄OH and the organic layer was separated and washed with brine (50 mL), dried (over anhydrous Na₂SO₄), and concentrated under reduced pressure. The crude material was

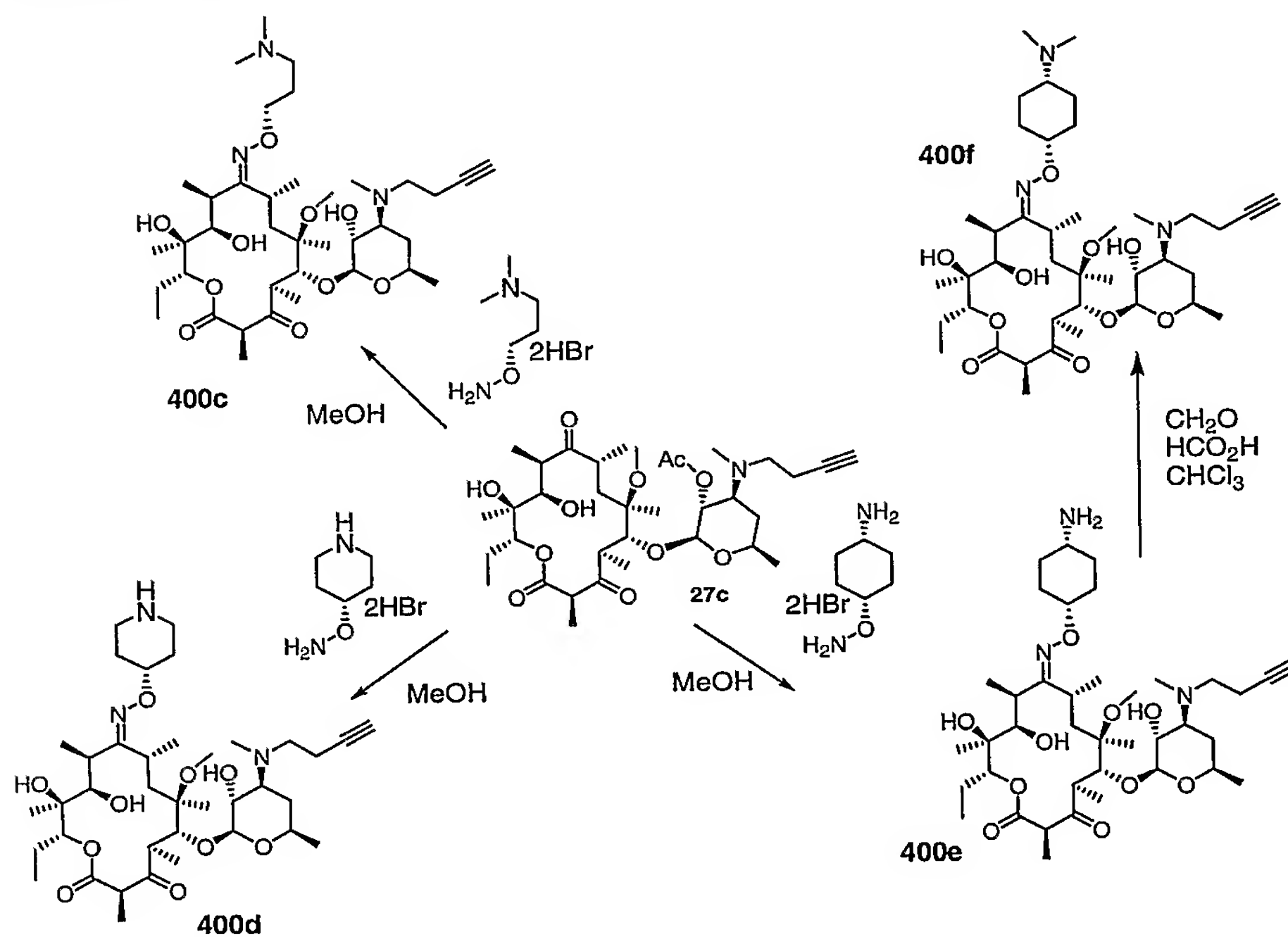
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purified by flash chromatography (silica gel, 12:1 CH₂Cl₂ and 2M methanolic ammonia) to yield 2g (78%) of the oxime **400a** as a 1:1 mixture of E/Z isomers. Data for **400a**: MS (ESI) *m/e* 724.7 (M+H)⁺.

5 Synthesis of oxime **400b**

Oxime **400b** was synthesized from alkyne **27c** and (R)-N-Pyrrolidin-3-yl-hydroxylamine hydrobromide using the conditions described above for the synthesis of oxime **400a**. Data for **400b**: MS (ESI) *m/e* 710.6 (M+H)⁺.

10 Scheme 108



Synthesis of oxime **400c**

Oxime **400c** was synthesized from alkyne **27c** and N-[2-(dimethylaminoethyl)]-hydroxylamine hydrobromide using the conditions described above for the synthesis of oxime **400a**. Data for **400b**: MS (ESI) *m/e* 726.5 (M+H)⁺.

Synthesis of oxime 400d

Oxime **400d** was synthesized from alkyne **27c** and *N*-Piperidin-4-yl-hydroxylamine hydrobromide using the conditions described above for the synthesis of oxime **400a**. Data for **400d**: MS (ESI) *m/e* 724.6 (M+H)⁺.

5 Synthesis of oxime 400e

Oxime **400e** was synthesized from alkyne **27c** and *cis*-4-aminocyclohexyl-hydroxylamine hydrobromide using the conditions described above for the synthesis of oxime **400a**. Data for **400e**: MS (ESI) *m/e* 738.7 (M+H)⁺.

10 Synthesis of oxime 400f

To a solution of oxime **400f** (20 mg, 0.02 mmol) in CHCl₃ (0.2 mL) was added formaldehyde (5 mg of 37% aqueous solution, 0.06 mmol) and formic acid (6 mg, 0.12 mmol). The mixture was heated at 50 °C in a sealed tube for 12h. The reaction mixture was partitioned between aqueous NaHCO₃ (10 mL) and chloroform (10 mL) the organic fraction was dried on
15 K₂CO₃, filtered and concentrated to give alkyne **400f** as a white solid (18 mg). Data for **400f**: MS (ESI) *m/e* 766.7 (M+H)⁺.

Synthesis of oxime triazoles 425-431, and 439

These triazoles were synthesized from the alkyne **400a** and the azides indicated in Table
20 6 using the standard copper-promoted cycloaddition conditions as previously described.

Synthesis of oxime triazoles 432-434, and 444-445

These triazoles were synthesized from the alkyne **400b** and the azides indicated in Table
6 using the standard copper-promoted cycloaddition conditions as previously described.
25

Synthesis of oxime triazoles 437 and 438

These triazoles were synthesized from the alkyne **400c** and the azides indicated in Table
6 using the standard copper-promoted cycloaddition conditions as previously described.

Synthesis of oxime triazoles 440 and 441

These triazoles were synthesized from the alkyne **400d** and the azides indicated in Table 6 using the standard copper-promoted cycloaddition conditions as previously described.

5 Synthesis of oxime triazole 443

These triazoles were synthesized from the alkyne **400e** and the azide 14w using the standard copper-promoted cycloaddition conditions as previously described.

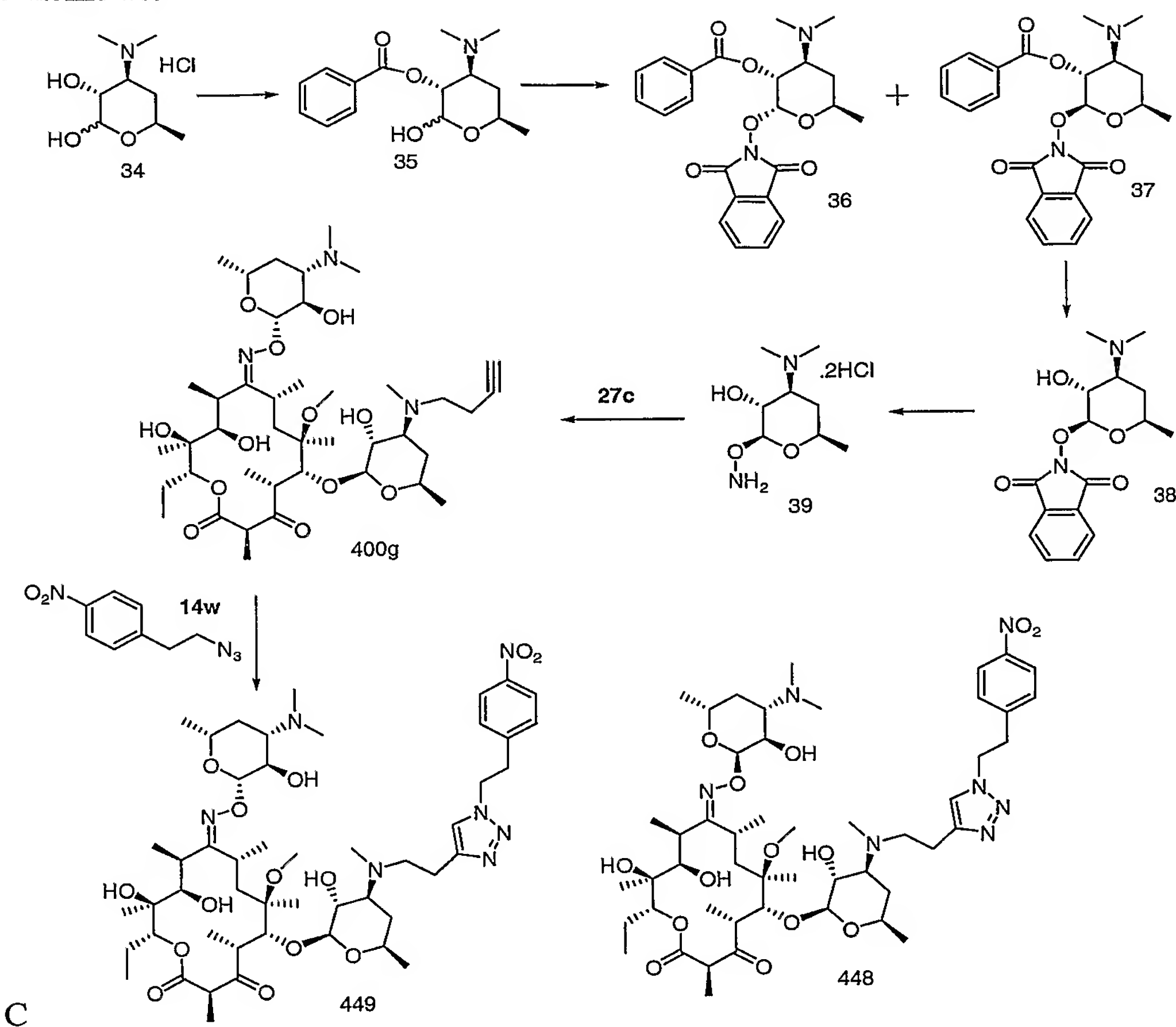
Synthesis of oxime triazole 448

10 These triazoles were synthesized from the alkyne **400f** and the azide 14w using the standard copper-promoted cycloaddition conditions as previously described.

Synthesis of compound 448 and 449

15 Compound **449** was synthesized from alkyne **400g**. This alkyne was derived from **27c** and intermediate **39** as shown in Scheme 109 below. *O*-desosaminyll hydroxylamine **39** was synthesized from desosamine HCl salt in four synthetic steps proceeding by benzyl ester protection of the 2' OH group, Mitsunobu reaction with *N*-hydroxyphthalimide, debenzylation and reduction of the phthalimide group.

Scheme 109



Synthesis of 34:

Desosamine hydrochloride was prepared according to literature (*JACS*, **1954**, 76, 3121-3131) procedure.

Synthesis of 35:

To a suspension of **34** (3.5 g, 16.5 mmol) in acetone (100 mL) was added K₂CO₃ (4.6 g, 33.1 mmol) and stirred for 30 minutes. Then was added benzoic anhydride (4.5 g, 19.8 mmol) and stirred for 16h at ambient temperature. The reaction mixture was diluted with CH₂Cl₂ (100 mL) and water (100 mL). Organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic layer was dried, concentrated and purified by flash chromatography over silica gel (50 % acetone in hexane). Yield 2.8 g (61 %). The compound **35** was isolated as a mixture of anomers and used for the next step without further purification. Data for **35** (mixture of anomers): ¹H NMR (300 MHz, CDCl₃): δ 1.22 (d, 1.5H), 1.30 (d, 1.5H), 1.40-1.54 (m, 1H), 1.80 (m, 1H), 2.32 (s, 3H), 2.34 (s, 3H), 2.95-3.04 (m, 1H), 3.31-3.40 (m, 0.5H),

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3.63-3.72 (m, 0.5H), 4.19-4.27 (m, 0.5H), 4.67 (d, 0.5H), 4.98 (dd, 0.5H), 5.16 (dd, 0.5H), 5.43 (d, 0.5H), 7.43 (t, 2H), 7.57 (t, 1H), 8.07 (t, 2H).

Synthesis of 36-37:

5 To solution of **35** (2.7 g, 9.7 mmol), *N*-hydroxyphthalimide (1.7 g, 10.7 mmol) and Ph_3P (2.8 g, 10.7 mmol) in THF was added DIAD (2.1 mL, 10.7 mmol) at 0°C and stirred at ambient temperature for 12h. The resulting solution was concentrated under reduced pressure and the crude material was redissolved in EtOAc (100 mL). This organic layer was washed with 1N NaOH (2 x 75 mL), water (1 x 75 mL) and brine (2 x 75 mL). It was dried (anhydrous Na_2SO_4),
10 concentrated and purified by flash chromatography over silica gel (30 % acetone in hexane) to gave **36** (0.9 g) and **37** (1.8 g) as anomers. Data for **4**: ^1H NMR (300 MHz, CDCl_3): δ 1.33 (d, 3H), 1.69 (dd, 1H), 1.84 (ddd, 1H), 2.34 (s, 6H), 3.02 (ddd, 1H), 3.67 (dq, 1H), 5.16 (d, 1H), 5.45 (dd, 1H), 7.50 (t, 2H), 7.55 (d, 1H), 7.71 (dd, 2H), 7.81 (dd, 2H), 8.19 (d, 2H).

Synthesis of 38:

15 A solution of **37** (1.8g) in MeOH (50 mL) was stirred at ambient temperature for 12h. The resulting solution was concentrated under reduced pressure and the crude material thus obtained was purified by flash chromatography over silica gel (50% acetone in hexane) to gave 0.6 g of **38**.

20

Synthesis of 39:

Hydrazine (0.514 mL, 16.4 mmol) was added to a solution of **38** (0.55 g, 1.64 mmol) in EtOH (5 mL) and heated to 60°C for 1h. Then the white suspension was stirred for 12h at ambient temperature. The white material was filtered and washed with MeOH (3 x 20 mL). The
25 combined filtrate was concentrated and purified by flash chromatography over silica gel (CH_2Cl_2 : 2 % NH_3 -MeOH = 9 :1) to gave 0.155 g of pure base which converted to hydrochloride salt **39** using 2M HCl.

Synthesis of 400g:

30 A solution of **39** (0.82 mmol) and macrolide alkyne **27c** (0.493 g, 0.74 mmol) in EtOH (3 mL) was heated to 60°C for 72h. Then the solution was concentrated and purified by flash

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chromatography over silica gel (CH_2Cl_2 : 2 % NH_3 -MeOH = 10 :1) to gave **400d** (0.08 g) as white solid. MS (ESI) m/e 799 ($\text{M}+\text{H}$)⁺, 400 ($\text{M}+2\text{H}$)⁺.

Synthesis of 449:

5 To a mixture of **400d** (0.0275g, 0.034 mmol), **14w** (0.001g, 0.052 mmol) and CuI (0.007 g, 0.034 mmol) was added THF (2 mL) under argon atmosphere. Then was added few drops of Hunig's base and stirred at ambient temperature for 2h. The reaction mixture was quenched with saturated NH_4OH solution containing 20% NH_4OH (10 mL) and stirred for 30 mins at ambient temperature. The mixture was extracted with methylene chloride (3 x 20 mL) and the combined
10 organic extract was washed with saturated ammonium chloride solution containing 10% ammonium hydroxide (1 x 50 mL). The resulting solution was dried with anhydrous Na_2SO_4 , concentrated and purified by flash chromatography over silica gel (CH_2Cl_2 : 2 % NH_3 -MeOH = 10:1) to gave 0.023 g of **449**. MS (ESI) m/e 496 ($\text{M} + 2\text{H}$)²⁺; ¹H NMR (300 MHz, CDCl_3 , partial): δ 0.85 (t, 3H), 1.05 (d, 3H), 1.15 (d, 3H), 3.33 (t, 2H), 3.81 (d, 1H), 4.10-4.28 (m, 3H),
15 4.58 (d, 2H), 4.84 (d, 1H), 5.20 (d, 1H), 7.08 (s, 1H), 7.24 (d, 2H), 8.14 (d, 2H).

Synthesis of 448:

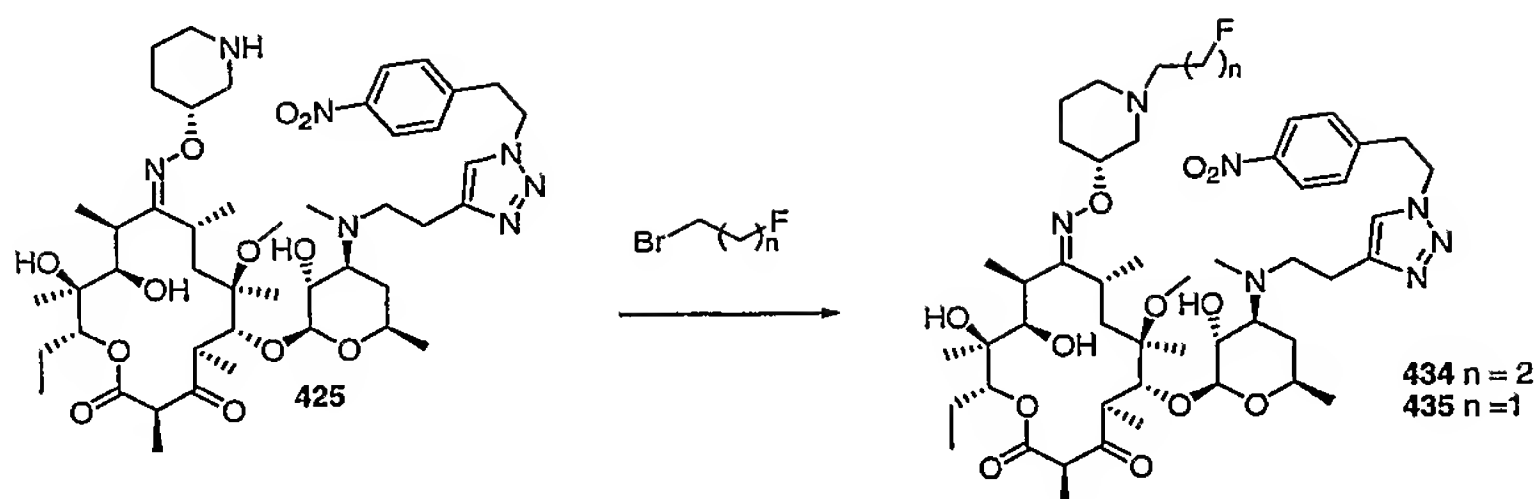
The compound **448** was synthesized from intermediate **36** using the same chemical sequences as described for **449**. Data for **448**: MS (ESI) m/e 496 ($\text{M} + 2\text{H}$)²⁺.

20

Oximes **434** and **435** were synthesized from compound **425** by alkylation of the nitrogen of the piperidinyloxime with 3-bromo-1-fluoropropane or 2-bromofluoroethane respectively as shown in Scheme 110 below.

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Scheme 110

**Synthesis of 434**

- 5 A solution of oxime **425** (0.04 g, 0.04 mmol) and 3-bromo-1-fluoropropane (0.012 mL, 0.13 mmol) in DMF (0.8 mL) was heated at 60°C for 14 h. The reaction mixture was diluted with water (20 mL) and brine (10 mL) and extracted with CH₂Cl₂ (3 x 30 mL) the combined organic extracts were dried (Na₂SO₄), filtered and concentrated. The crude material was purified by flash chromatography (silica gel, 3:100:0.1 MeOH / CH₂Cl₂ / NH₄OH) to yield 0.023g of the oxime
- 10 **434**. Data for **434**: MS (ESI) *m/e* 489.1 (M+2H)²⁺.

Synthesis of 435

- Compound **435** was synthesized from compound **425** and 2-bromofluoroethane under the conditions described for the synthesis of compound **434**. Data for **435**: MS (ESI) *m/e* 482.1
- 15 (M+2H)²⁺.

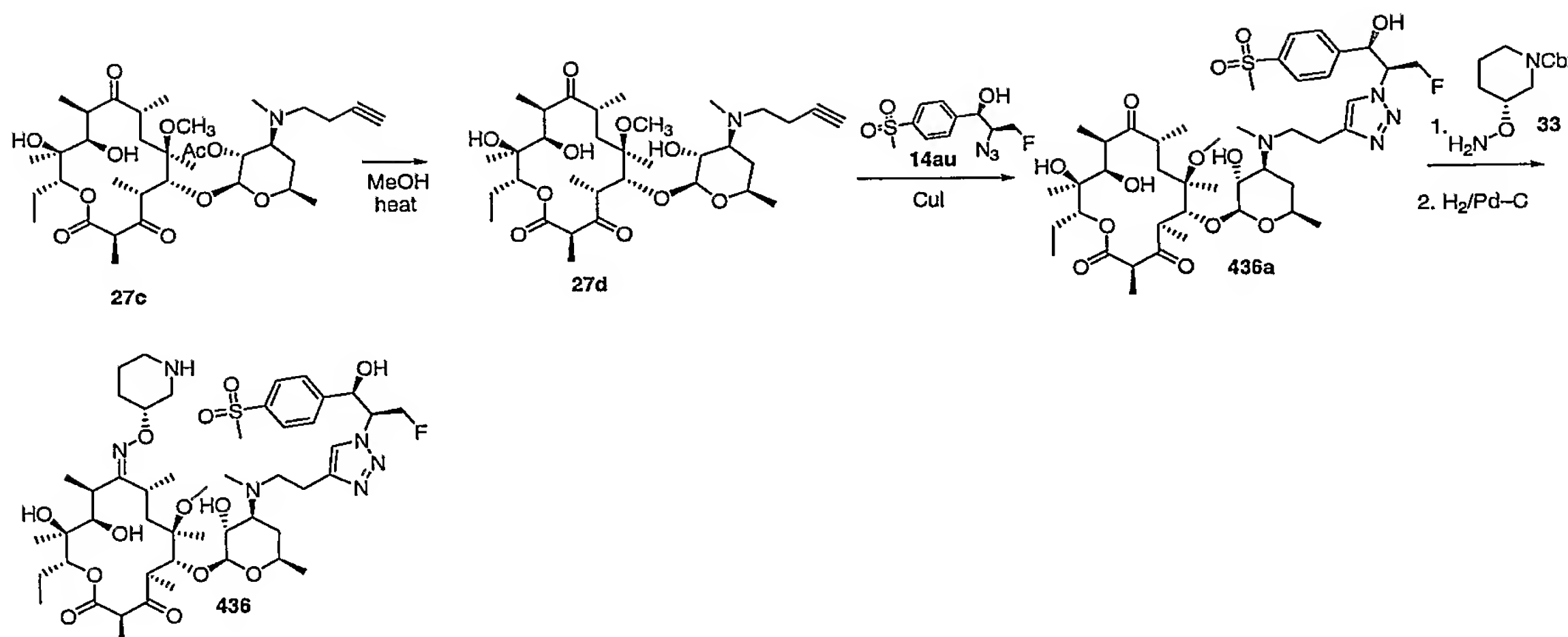
 Compound **436** was prepared via a different approach by oximation after cycloaddition as shown in Scheme 110.

20 Synthesis of Compound 436

- Scheme 111 below depicts the synthesis of compound **436** starting from alkyne **27c**. Deacylation of **27c** in methanol provided alkyne **27d**, which was treated with azide **14au** to provide triazole **436a**. This triazole was treated with 3(R)-Hydroxyamino-piperidine-1-carboxylic acid benzyl ester to give the carbobenzoxy (CBZ)-protected oxime as a mixture of
- 25 E/Z isomers. The CBZ group was removed by hydrogenolysis to afford compound **436**.

Scheme 111

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Synthesis of alkyne 27d

A solution of ketolide **27c** (0.230 g) in MeOH (10 mL) was heated at 50°C for 48 h. The solvent was removed under reduced pressure to yield pure deacetylated product **27d** (0.190 g, 88%). Data for **27d**: MS (ESI) *m/e* 626 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): TM 0.85 (t, 3H), 2.25 (s, 3H), 2.70 (s, 3H), 2.97 (q, 1H), 3.10 (t, 1H), 3.18 (dd, 1H), 3.5 (m, 1H), 3.80-3.97 (m, 2H), 4.32 (m, 2H), 5.15 (dd, 1H).

Synthesis of 436a

Triazole **436a** was synthesized from alkyne **27d** and azide **14au** using the copper catalyzed cycloaddition conditions disclosed for the compounds of Table 1 above.

Synthesis of 436

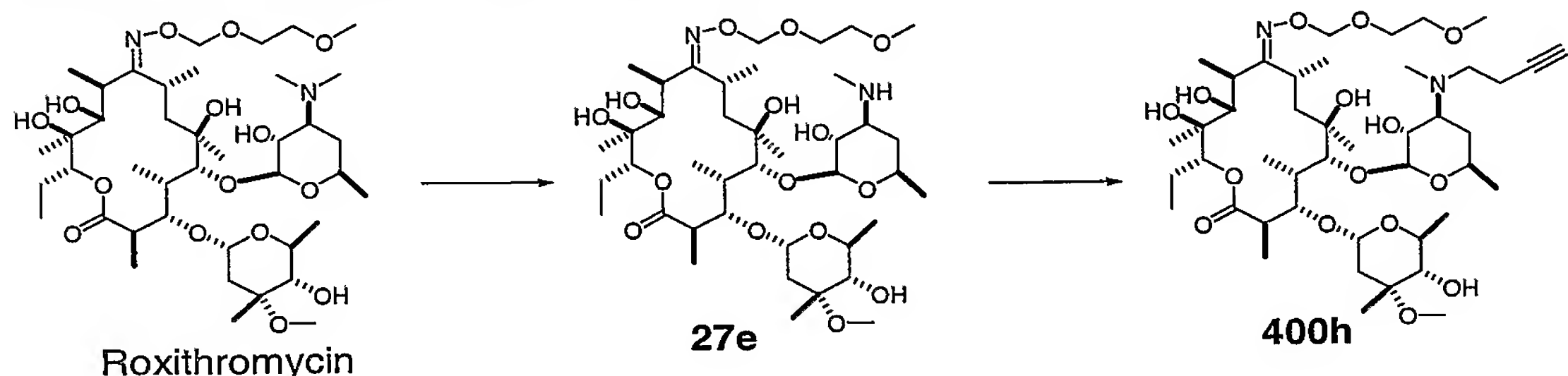
A solution of alkoxyamine **33** (0.13 g, 0.50 mmol) in ethyl ether (1.0 mL), was treated with 2.0 M hydrogen chloride in ethyl ether (1.5 mL, 3.0 mmol), stirred at 23 °C for 1 h, and evaporated to a white foam. A solution of this hydrochloride salt in ethanol (3.5 mL) was treated with **436a** (0.15 g, 0.17 mmol) and the reaction mixture stirred at 55 °C for 16 h, and then cooled to room temperature and diluted with H₂O (30 mL). Ammonium hydroxide was added to adjust the pH to 10, and the reaction mixture was extracted with ethyl acetate (3 × 30 mL), dried (Na₂SO₄), and evaporated to a yellow oil.

A solution of the crude CBZ-protected intermediate in ethanol (10 mL) was treated with 10% Pd/C (100 mg) and the reaction mixture was stirred at 23 °C for 12 h under a balloon of hydrogen. Filtration and evaporation provided crude material which was purified by preparative

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thin-layer chromatography (SiO₂, 10% 2M NH₃-methanol/dichloromethane) to provide **436** (80 mg, 0.080 mmol) as a white solid: LCMS (ESI) *m/e* 550 (M+2H)²⁺.

Scheme 112 Synthesis of intermediate 400h



5

Synthesis of compound 27e

To a mixture of Roxithromycin (850mg, 0.914mmol, 90%) and NaOAc (828mg, 10.000mmol) in a mixture of MeOH (6.0mL) and water (1.5mL) at 48°C was added I₂ in four portions (each portion: 63.5mg) over 30min, after each portion I₂, followed by 1N NaOH (400μL). The reaction was continued for 30min. The solvent was removed and EtOAc (100mL) was added, followed by water (20mL). The organic phase was washed with brine (40mLX2), dried with Na₂SO₄. The residue was separated by flash chromatography (FC) (6/94/0.2 MeOH/CH₂Cl₂/NH₄OH), giving 600mg compound **27e** in 80% yield.

LCMS (ESI) *m/e* 824 (M+H)⁺.

15

Synthesis of compound 400h

A mixture of compound **27e** (500mg, 0.608mmol) and toluene-4-sulfonic acid but-3-ynyl ester in a mixture solvents of THF (5.4mL) and Hunig's base (1.6mL) was refluxed for 48hr. The reaction mixture was concentrated, then, EtOAc (100mL) was added. The organic layer was washed with saturated NaHCO₃ (20mL), and brine (50mL). Compound **400h** was isolated by FC (3/100/0.2 MeOH/CH₂Cl₂/NH₄OH), gave 316mg in 59% yield.

LCMS (ESI) *m/e* 876 (M+H)⁺.

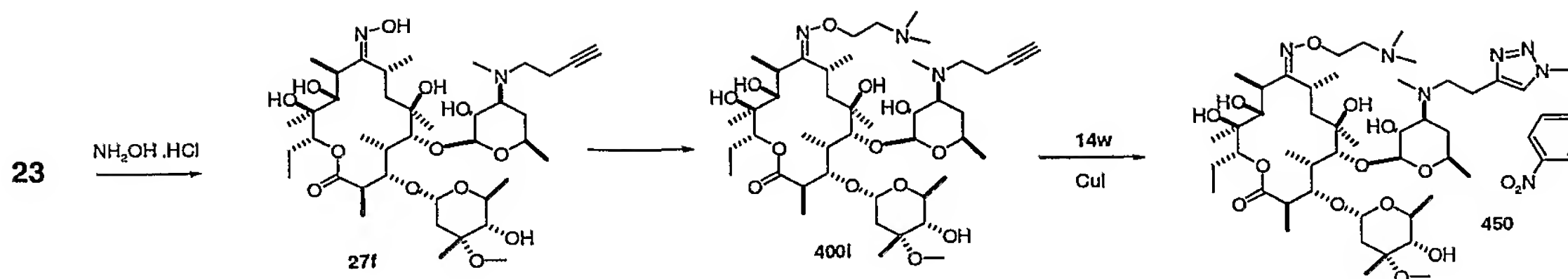
Synthesis of compound 447

This compound was synthesized from alkyne **400h** and azide **14bt** using the conditions described in Example 1.

Scheme 113

25

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Synthesis of compounds 450 and 451

- 5 A mixture of 9-oxime compound **27f** (100mg, 0.125mmol), NaCO_3 (106mg, 0.998mmol) and 2-chloroethyldimethylamine HCl salt (109mg, 0.749mmol) in acetone (1.0mL) in seal tube was stirred at 70°C for 5 days, then, EtOAc (30mL) was added washed with 1N NaOH (2mL) and water (15mL), Compound **400h** was isolated by FC (3/100/0.2 MeOH/ CH_2Cl_2 / NH_4OH), gave 75mg in 70% yield.
- 10 MS (ESI) m/e 859 ($\text{M}+\text{H}$)⁺.

Triazole **450** was synthesized from alkyne **400i** and azide **14w** using the conditions of Example 1.

Synthesis of alkyne 400j

- 15 To a mixture of 9-oxime compound **27f** (180mg, 0.229mmol), 3-fluoropropyl bromide (161mg, 1.144mmol) and Bu_4NBr (37mg, 0.115mmol) in CH_2Cl_2 (9.0mL) was added 50% NaOH (3.0mL). The mixture was stirred at room temperature for 45min, then, water (20mL) was added. The aqueous phase was extracted with CH_2Cl_2 (20mL X 2). The combined organic layers were washed with brine (50mL). Compound **400j** was isolated by FC (25/75/0.2 Acetone/Hexane/ NH_4OH), gave 94mg in 48% yield. MS (ESI) m/e 848 ($\text{M}+\text{H}$)⁺.
- 20

Triazole **451** was synthesized from oxime alkyne **27f** and alkyne **400j** by alkylation with 3-fluoro-1-bromo propane followed by cycloaddition with azide **14w** as described for the synthesis of compound **450**.

Table 5

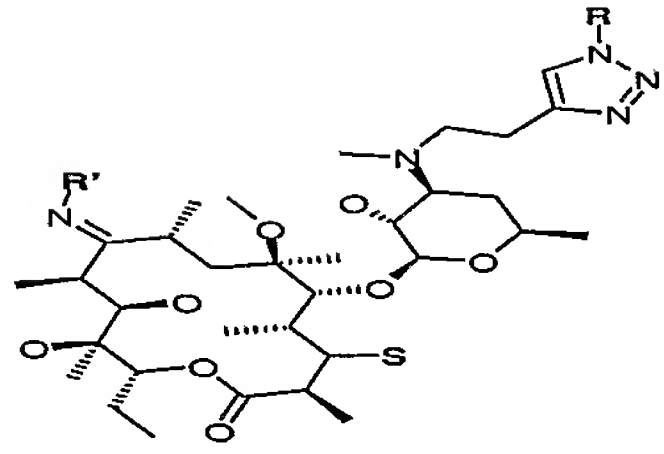
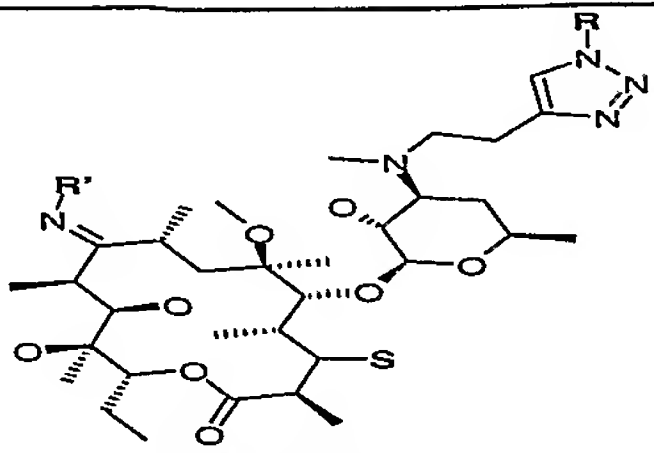
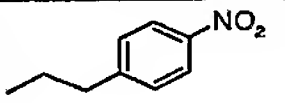
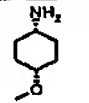
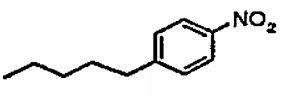
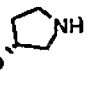
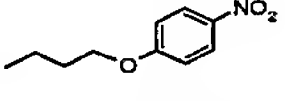
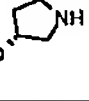
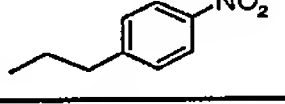
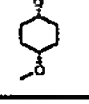
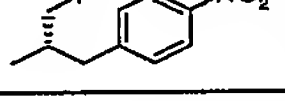
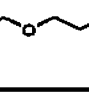
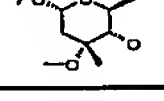
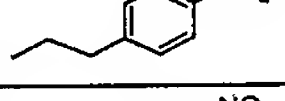
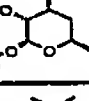
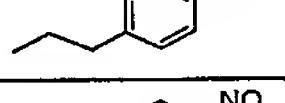
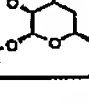
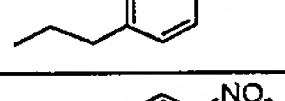
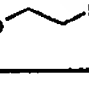
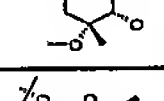
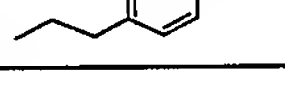
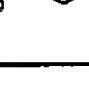
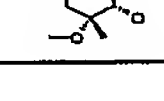
					
Compound	R	R'	S	Azide	LCMS (M/Z)
425			=O	14w	459.0 (M + 2H) ²⁺ 919.9 (M + H) ⁺
426			=O	14au	459.0 (M + 2H) ²⁺ 919.9 (M + H) ⁺
427			=O	14b	476.0 (M + 2H) ²⁺
428			=O	14be	469.0 (M + 2H) ²⁺ 936.7 (M + H) ⁺
429			=O	14bd	452.0 (M + 2H) ²⁺
430			=O	14v	474.1 (M + 2H) ²⁺
431			=O	14bq	451.1 (M + 2H) ²⁺ 902.7 (M + H) ⁺
432			=O	14w	467.0 (M + 2H) ²⁺ 932.8 (M + H) ⁺
433			=O	14bq	444.9 (M + 2H) ²⁺ 888.6 (M + H) ⁺
434			=O	n/a	489.1 (M + 2H) ²⁺
435			=O	n/a	482.1 (M + 2H) ²⁺
436			=O	14w	550 (M + 2H) ²⁺
437			=O	14ej	467 (M + 2H) ²⁺ 933 (M + H) ⁺
438			=O	14w	453 (M + 2H) ²⁺ 905 (M + H) ⁺
439			=O	14ej	473 (M + 2H) ²⁺ 945 (M + H) ⁺
440			=O	14w	459 (M + 2H) ²⁺ 917 (M + H) ⁺
441			=O	14b	476 (M + 2H) ²⁺ 951 (M + H) ⁺
442			=O	14w	918 (M + H) ⁺

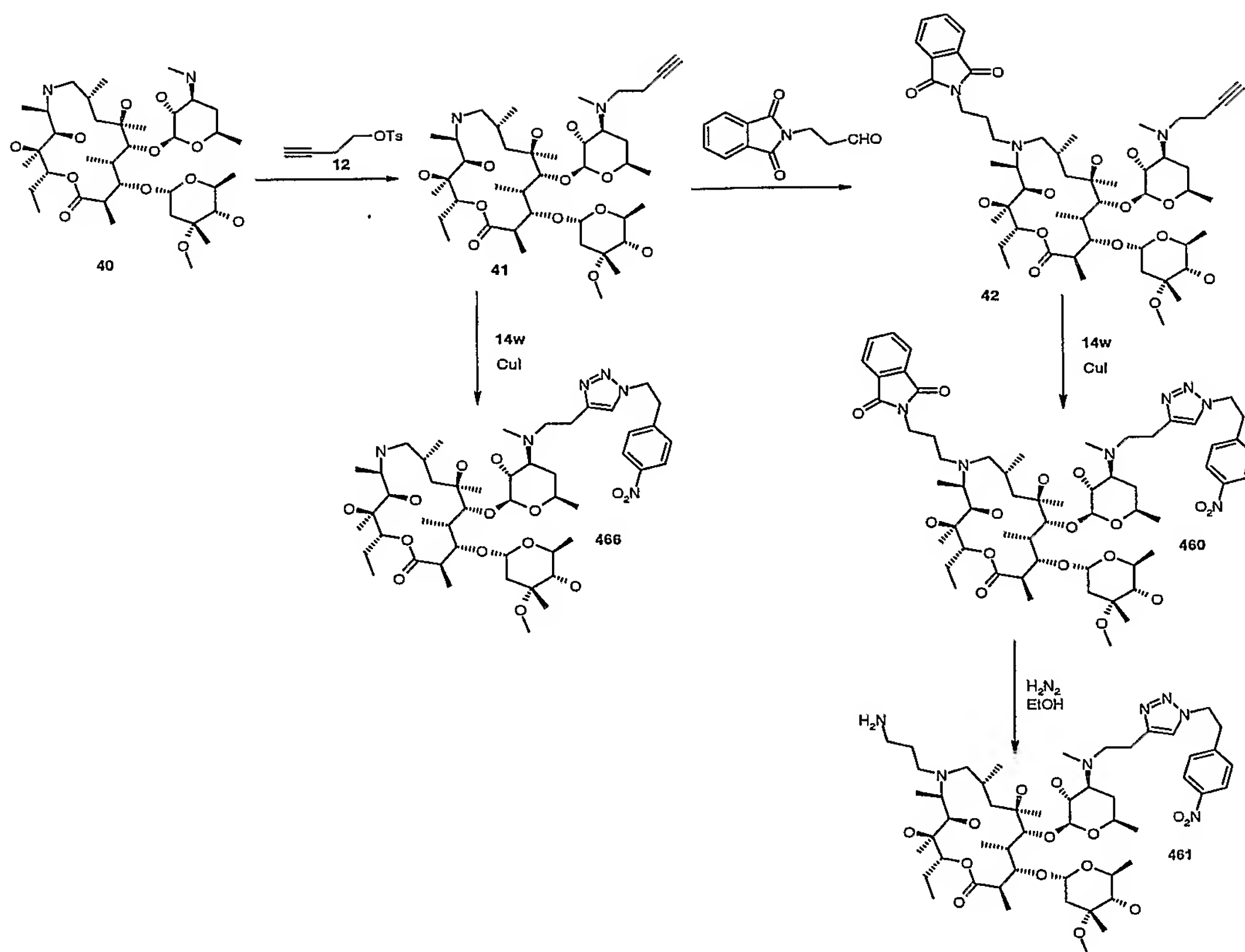
Table 5 continued

					
Compound	R	R'	S	Azide	LCMS (M/Z)
443			=O	14w	466 (M + 2H) ²⁺ 931 (M + H) ⁺
444			=O	14ej	466 (M + 2H) ²⁺ 930.8 (M + H) ⁺
445			=O	14et	467 (M+2H) ²⁺
446			=O	14w	480 (M + 2H) ²⁺ 959 (M + H) ⁺
447				14bt	550 (M + 2H) ²⁺ 1100 (M + H) ⁺
448			=O	14w	496 (M+2H) ²⁺
449			=O	14w	496 (M+2H) ²⁺
450				14w	526 (M + 2H) ²⁺ 1051 (M + H) ⁺
451				14w	520 (M + 2H) ²⁺ 1040 (M + H) ⁺

Example 5 Synthesis of compounds 460-466

- 5 Alkyne **41** shown in Scheme 114, was derived from 9' N-desmethyl azithromycin under conditions identical to those described in Example 1 for the synthesis of Alkyne **4** above. This alkyne was the common intermediate for all of the compounds in Table 6. Compound **466** was derived directly from alkyne **41** by copper promoted [3 +2] cycloaddition with azide **14w** using the conditions of Example 1.

Scheme 114



Synthesis of alkyne 41

5 A solution of 5.0 g (6.93 mmol) of 3',9'-bis-*N*-desmethyl azithromycin **40** and 3.107 g (13.80 mmol) of tosylate **11** in 60 mL of Hunig's base and 8 mL of acetonitrile was heated to 100 °C for 24 h. After cooling, the solvents were removed by rotary evaporation, and the residue was purified through silica gel column chromatography to give 1.70 g of final product. MS (ESI) m/e 774 ($\text{M}+\text{H}$)⁺.

10

Synthesis of Compound 42

A solution of 0.200 g (0.26 mmol) of **41**, 0.262 g (1.29 mmol) of 3-(*N*-phthalimidyl)propionaldehyde, and 0.110 g (0.52 mmol) of $\text{NaB}(\text{OAc})_3\text{H}$ in 1.5 mL of DMF was stirred at 25 °C for 4 h. The reaction mixture was diluted with H_2O , extracted with CH_2Cl_2 (50 mL x 3), combined organic layers were washed with brine, dried over MgSO_4 , concentrated, purified

15

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through silica gel column chromatography to give 0.200 g of product. MS (ESI) *m/e* 961 (M+H)⁺.

Synthesis of triazole 460

5 A solution of 0.200 g (0.20 mmol) of alkyne **42**, 0.080 g (0.41 mmol) of azide **14w**, and 0.040 g (0.20 mmol) of CuI in 15 mL of THF was degassed, then put under argon. To it was added 0.2 mL of Hunig's base. The reaction was stirred at 25 °C for 6 h. Subsequently, to the mixture was added 40 mL of 10% NH₄OH, stirred for 10 min, extracted with CH₂Cl₂ (50 ml x 3), the combined organic layers were washed with brine, dried, concentrated, purified by preparative
10 TLC to give 0.098 g of compound **460**. MS (ESI) *m/e* 1153 (M+H)⁺.

Synthesis of triazole 461

 A solution of 0.025 g (0.02 mmol) of **RX-460** and 0.002 g (0.04 mmol) of hydrazine in 2.0 ml of ethanol was kept under refluxing for 6 h. After cooling down, ethanol was removed,
15 the residue was suspended in 5.0 mL of CH₂Cl₂, filtered through a cotton-stuffed pipette, and collected organic solvent was concentrated. This process was repeated a couple of more times if necessary until MS and proton NMR gave indications that the material was pure enough to give 0.020 g of final product. MS (ESI) *m/e* 1023 (M+H)⁺.

20 Synthesis of compounds 462 and 463.

 Compound **462** was synthesized from alkyne **41** and 2-(*N*-phthalimidyl)-acetaldehyde using the procedure described above for compound **460**.

 Compound **463** was synthesized from compound **462** using the conditions described
25 above for the synthesis of compound **461** from **460**.

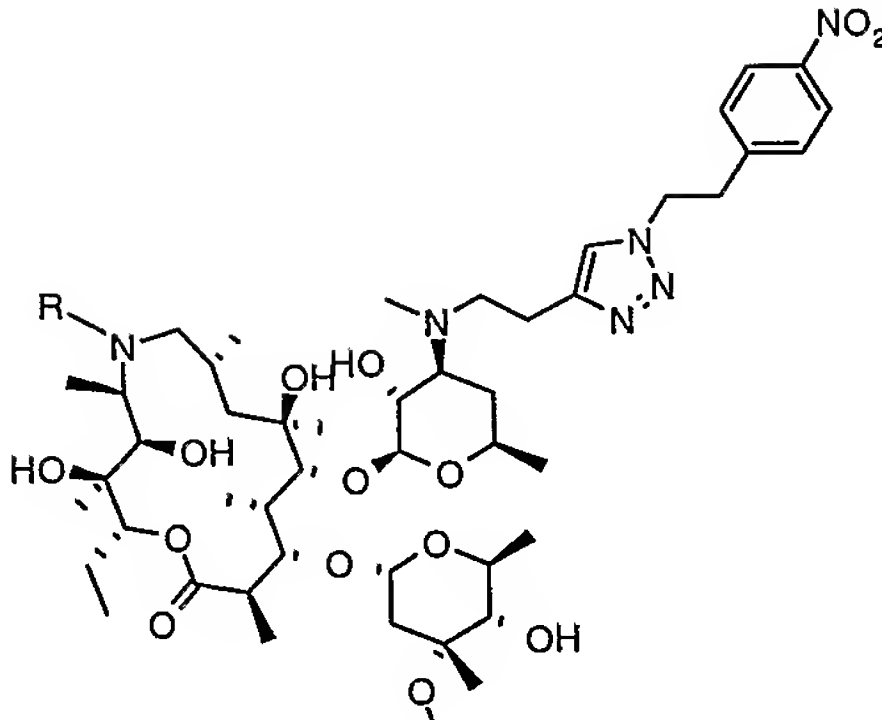
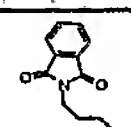
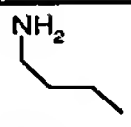
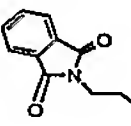
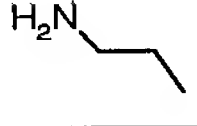
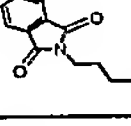

Synthesis of compounds 464 and 465.

 Compound **464** was synthesized from alkyne **41** and 4-(*N*-phthalimidyl)-butyraldehyde using the procedure described above for compound **460**.

30

 Compound **465** was synthesized from compound **464** using the conditions described above for the synthesis of compound **461** from **460**.

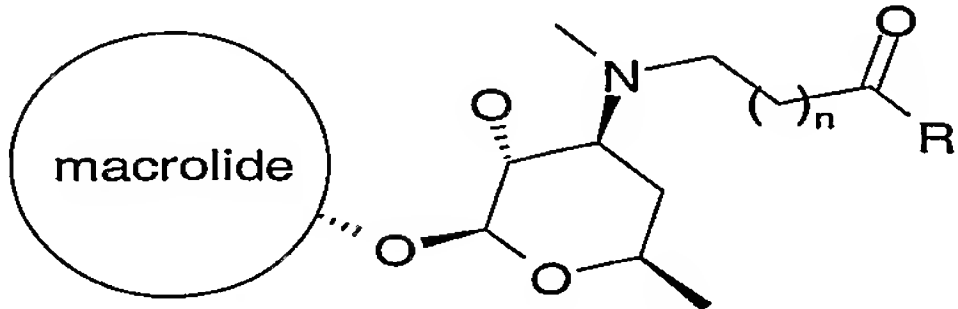
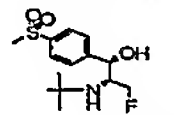
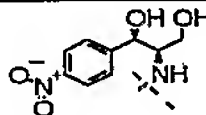
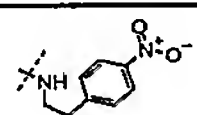
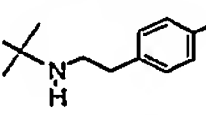
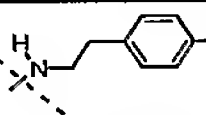
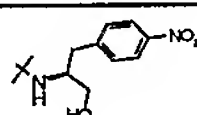
Table 6

		
Compound	R	LCMS (M/Z)
460		1153.0 (M + H) ⁺
461		1023.0 (M + H) ⁺
462		1138.0 (M + H) ⁺
463		1009 (M + H) ⁺
464		1167.0 (M + H) ⁺
465		1037.0 (M + H) ⁺
466	H	966.1 (M + H) ⁺

Example 6 Synthesis of compounds 475-480

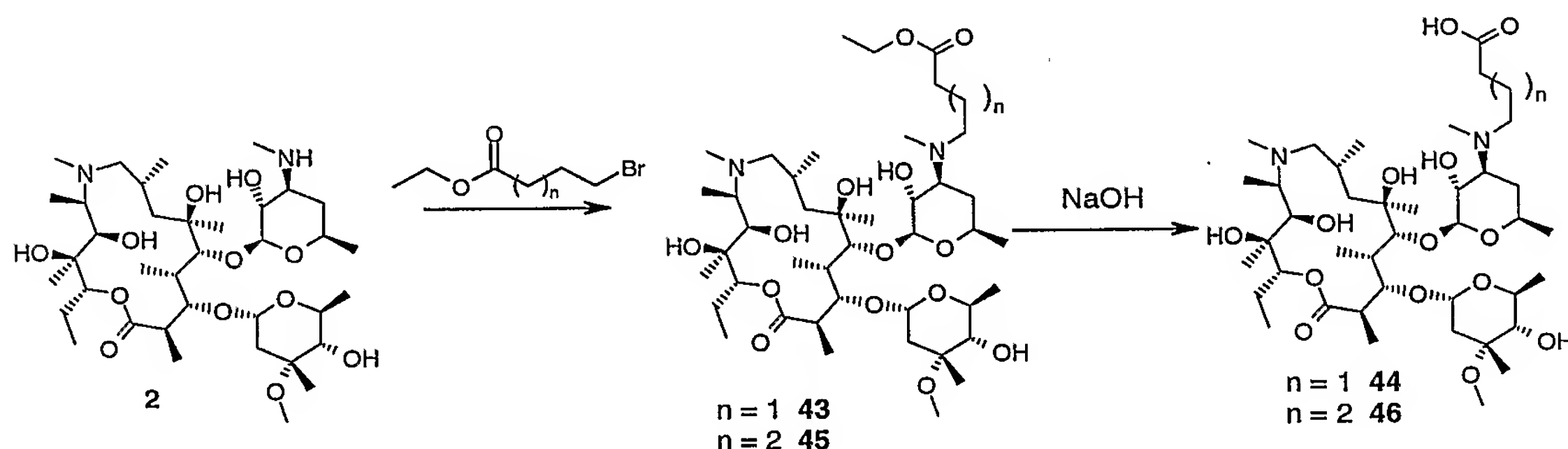
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Table 7

				
Compound	R	Macrolide	n	LCMS (M/Z)
475		Azithromycin	3	532.1 (M + 2H) ²⁺
476		Azithromycin	3	516.2 (M + 2H) ²⁺
477		Azithromycin	3	493 (M + 2H) ²⁺
478		Clarithromycin	2	941 (M + H) ⁺
479		Clarithromycin	1	927 (M + H) ⁺
480		Azithromycin	1	493.6 (M + 2H) ²⁺

As shown in Scheme 115 below, the precursor carboxylic acid derivatives **44** and **46** were readily synthesized from amine **2** by alkylation with appropriate omega bromoesters followed by saponification. These carboxylic acids were elaborated by amide coupling with appropriate amines to afford final compounds **475-477** and **480**

Scheme 115



Synthesis of compound **43**

A solution of desmethylazithromycin **2** (3.7 g, 5 mmol) in diisopropylethylamine (25 mL) was treated with ethyl 5-bromobutyrate (7.2 g, 50 mmol) and stirred at 105 °C for 5 h. The reaction mixture was cooled to room temperature, decanted, and the liquid portion evaporated to

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a yellow oil. Flash chromatography (SiO₂, 6% 2M NH₃-methanol/dichloromethane) provided **43** (2.7 g, 3.2 mmol) as a white foamy solid: LCMS (ESI) *m/e* 850 (M+H)⁺.

Synthesis of compound 44

5 A solution of **43** (0.60 g, 0.70 mmol) in methanol (16 mL) and H₂O (2.4 mL) was treated with 1.0 M aqueous sodium hydroxide (2.0 mL, 2.0 mmol) and stirred at 50 °C for 2.5 h. The reaction mixture was cooled to room temperature and quenched by the addition of acetic acid (0.12 mL, 2.0 mmol), and evaporated to a white powder. Flash chromatography (SiO₂, 10% 2M NH₃-methanol/dichloromethane) provided **44** (0.40 g, 0.49 mmol) as a white powder: LCMS (ESI) *m/e* 836 (M+Na)⁺.

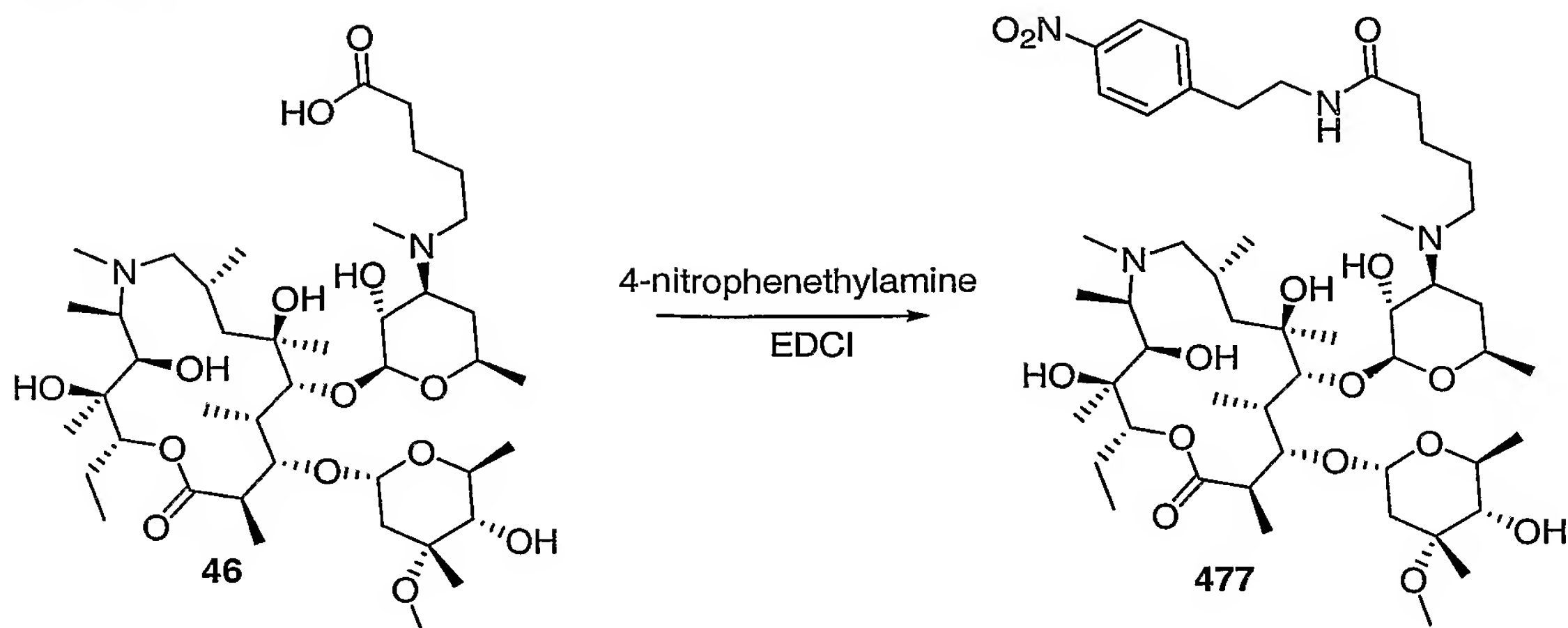
10 Synthesis of compound 45

A solution of desmethylazithromycin **2** (3.7 g, 5 mmol) in diisopropylethylamine (25 mL) was treated with ethyl 5-bromovalerate (5.2 g, 25 mmol) and stirred at 105 °C for 4 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (100 mL), washed with H₂O (100 mL), dried (Na₂SO₄) and evaporated. Flash chromatography (SiO₂, 6% 15 2M NH₃-methanol/dichloromethane) provided **45** (0.55 g, 0.64 mmol) as a colorless oil: LCMS (ESI) *m/e* 864 (M+H)⁺.

Synthesis of compound 46

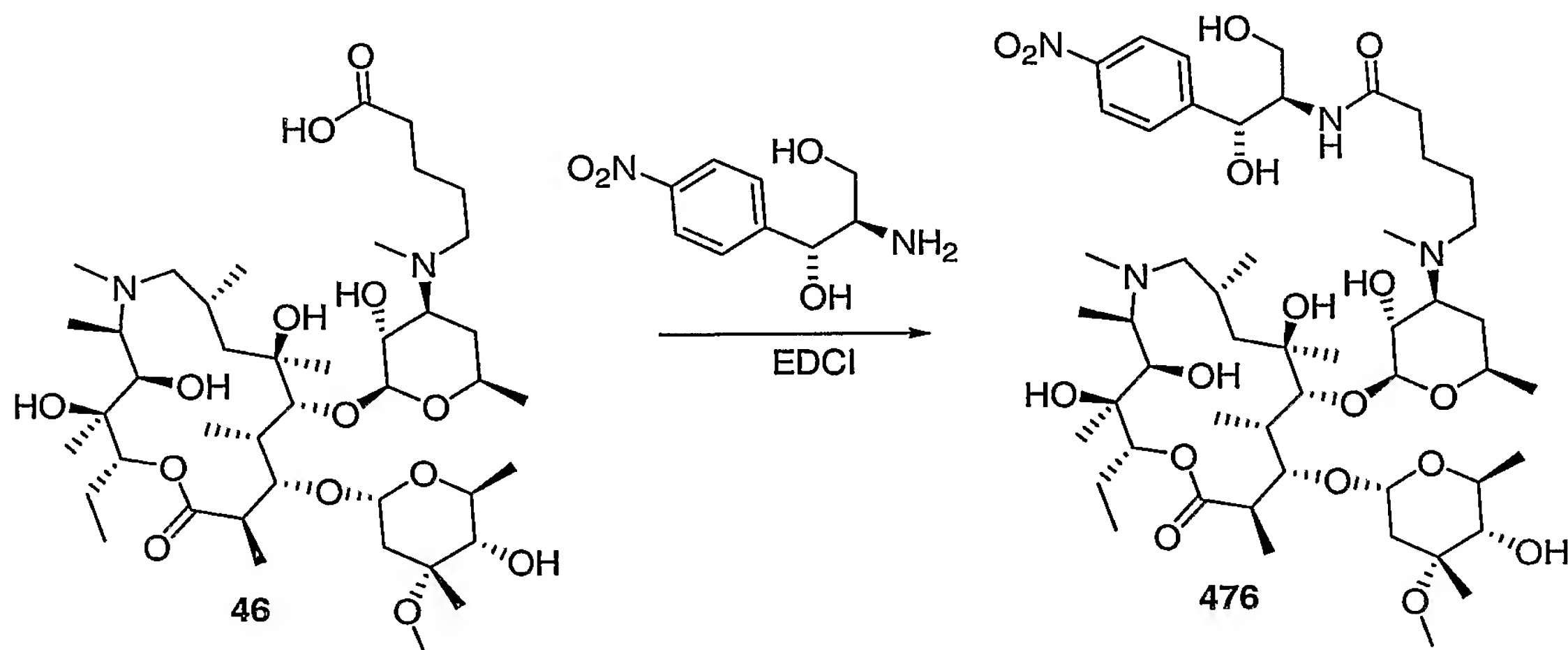
A solution of **45** (0.54 g, 0.62 mmol) in methanol (10 mL) and H₂O (1.25 mL) was treated with 1.0 M aqueous sodium hydroxide (1.25 mL, 1.25 mmol) and stirred at 45 °C for 2.5 20 h. The reaction mixture was cooled to room temperature and quenched by the addition of 1.0 M hydrochloric acid (1.25 mL, 1.25 mmol), extracted with dichloromethane (3 × 30 mL), dried (Na₂SO₄), and evaporated to provide **46** (0.52 g, 0.62 mmol) as a white powder: LCMS (ESI) *m/e* 836 (M+2H)⁺.

Scheme 116

**Synthesis of compound 477**

- 5 A solution of **46** (30 mg, 0.035 mmol) in dichloromethane (0.5 mL) was treated with 4-nitrophenethylamine hydrochloride (14 mg, 0.070 mmol), diisopropylethylamine (0.018 mL, 0.11 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (10 mg, 0.053 mmol), and stirred at 23 °C for 12 h. The reaction mixture was evaporated to a yellow film and purified by preparative thin-layer chromatography (SiO₂, 5% 2M NH₃-methanol/dichloromethane) to provide **477** (7.0
- 10 mg, 0.0071 mmol) as a white film: LCMS (ESI) *m/e* 493 (M+2H)²⁺.

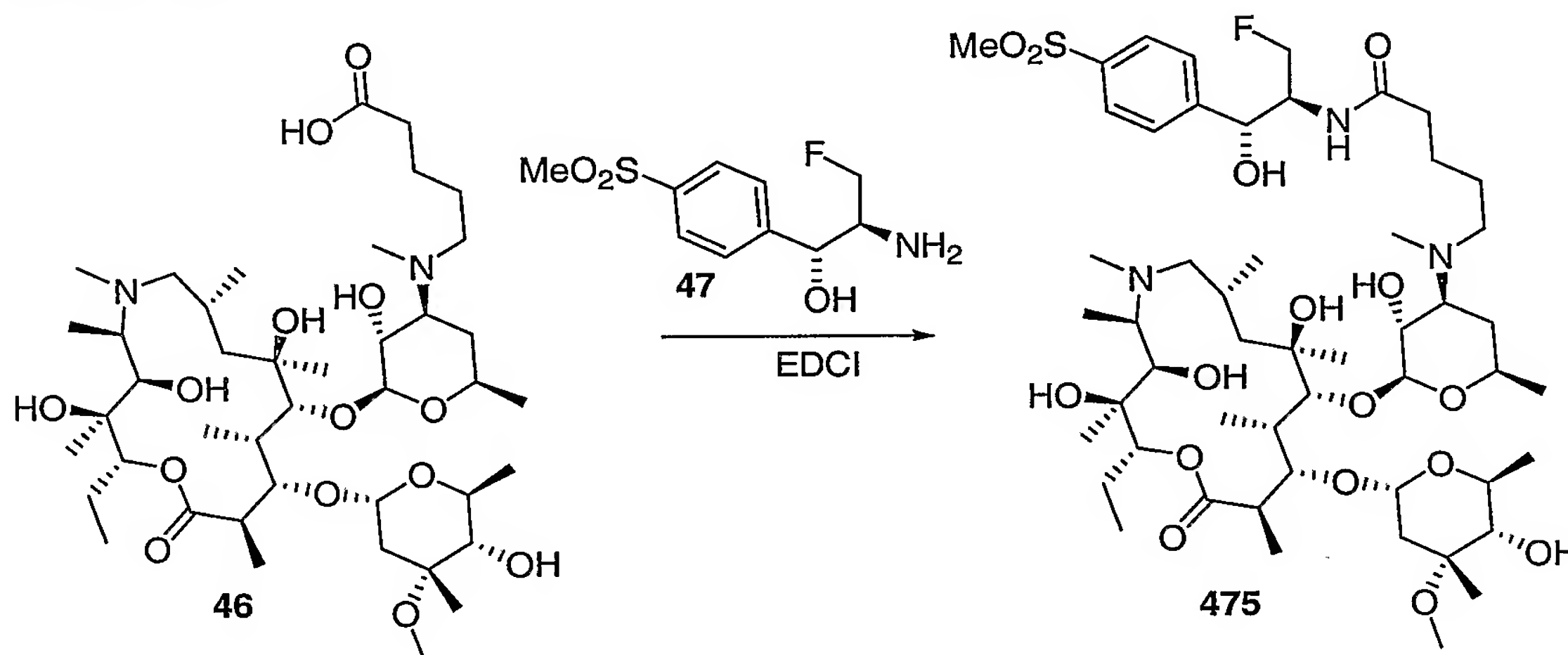
Scheme 117



- 15 A solution of **46** (31 mg, 0.037 mmol) in DMF (0.4 mL) was treated with D-(-)-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol (7.9 mg, 0.037 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (8.5 mg, 0.037 mmol), and stirred at 23 °C for 16 h. The reaction mixture was evaporated to a yellow film and purified by preparative thin-layer

chromatography (SiO₂, 5% 2M NH₃-methanol/dichloromethane) to provide **476** (10 mg, 0.0097 mmol) as a white solid: LCMS (ESI) *m/e* 516 (M+2H)²⁺.

Scheme 118



- 5 A solution of **46** (40 mg, 0.048 mmol) in CH₂Cl₂ (0.7 mL) was treated with Flofenicol amine **47** (12 mg, 0.048 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (10 mg, 0.053 mmol), and stirred at 23 °C for 16 h. The reaction mixture was evaporated to a yellow film and purified by preparative thin-layer chromatography (SiO₂, 5% 2M NH₃-methanol/dichloromethane) to provide compound **475** (8 mg, 0.008 mmol) as a white solid:
- 10 LCMS (ESI) *m/e* 532.1 (M+2H)²⁺.

Synthesis of compounds **478** and **479**

These compounds were synthesized from clarithromycin amine **21** ethyl 4-bromobutyrate or ethyl 3-bromopropionate and 4 fluorophenethyl amine using the chemistries described above for compound **477**.

15 Synthesis of compound **480**

Compound **480** was synthesized from amine **2** and bromide **48** as shown in Scheme 117 using the alkylating conditions described for the synthesis of alkyne **3** in Example 1.

Scheme 119

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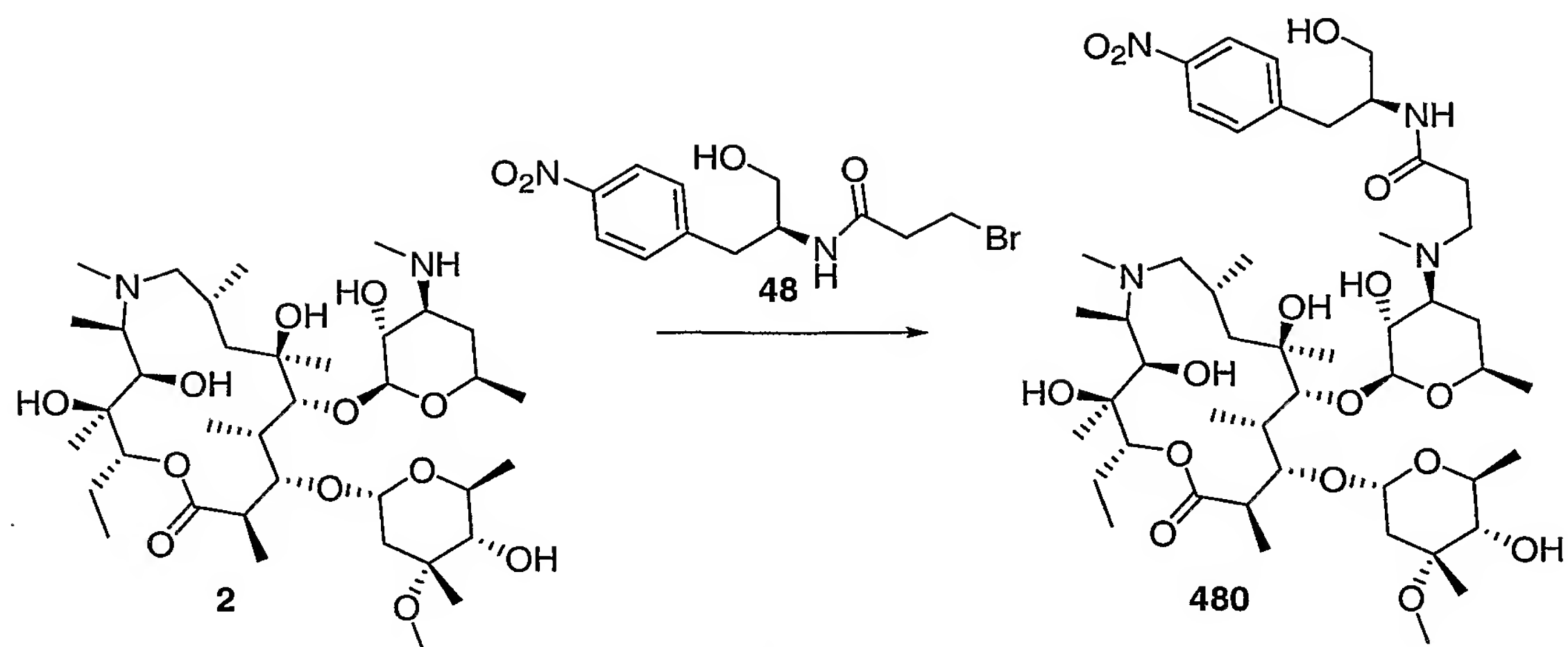
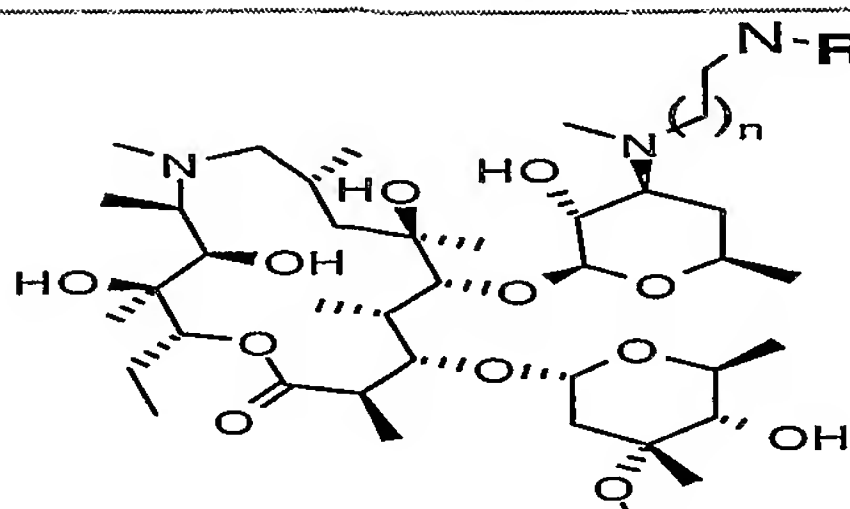
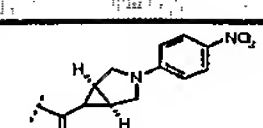
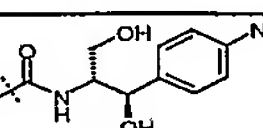
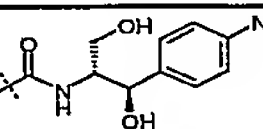
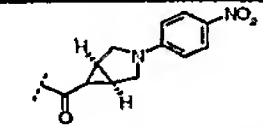
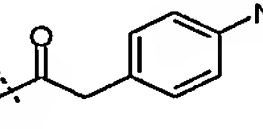
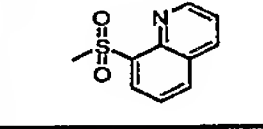
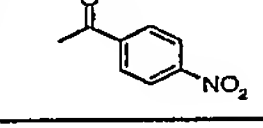
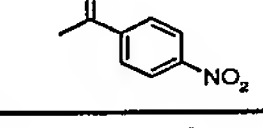
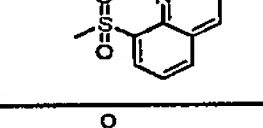
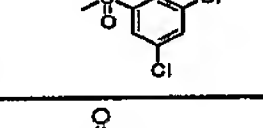
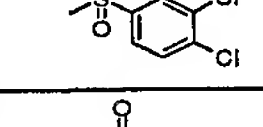
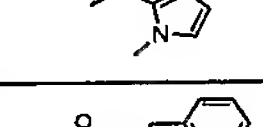
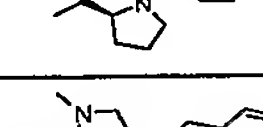
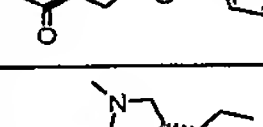
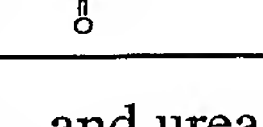
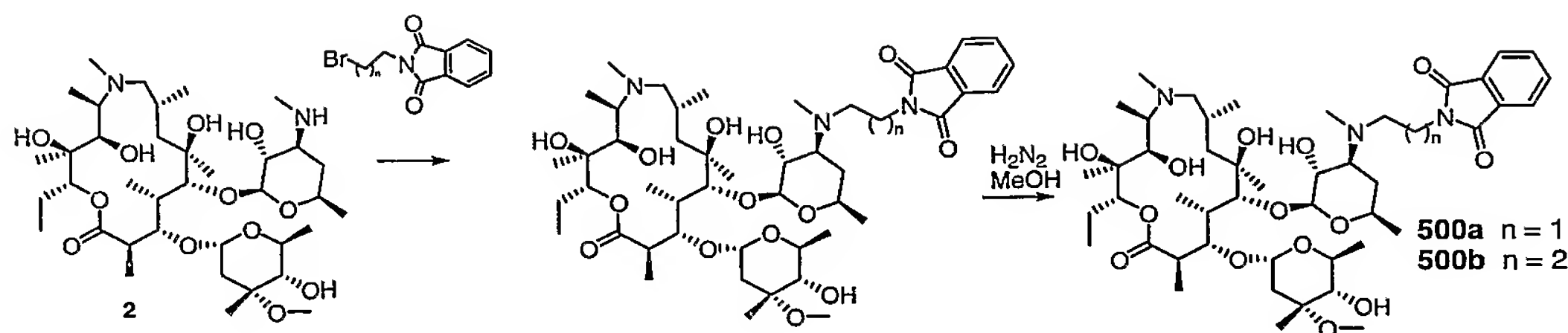
**Example 7 Synthesis of compounds 501-515**

Table 8

			
Compound	R	n	LCMS (M/Z)
501		2	505 (M + 2H) ²⁺
502		2	516 (M + 2H) ²⁺
503		1	509 (M + 2H) ²⁺
504		1	505 (M + 2H) ²⁺
505		1	471.7 (M + 2H) ²⁺
506		1	485.6 (M + 2H) ²⁺
507		1	464.6 (M + 2H) ²⁺
508		2	471.7 (M + 2H) ²⁺
509		2	492.7 (M + 2H) ²⁺
510		1	988.7 (M + H) ⁺
511		1	988.7 (M + H) ⁺
512		1	443.6 (M + 2H) ²⁺
513		1	483.7 (M + 2H) ²⁺
514		1	498.8 (M + 2H) ²⁺
515		1	466.6 (M + 2H) ²⁺

The amide-, sulfonamide-, and urea- linked derivatives **501-515** of Table 8 were synthesized from amines **500a** and **500b** by addition of suitable carboxylic acids, sulfonyl chlorides, or acyl imidazoles respectively under standard conditions. The amines **500a-b** were synthesized as shown in Scheme 120.

Scheme 120



Synthesis of amine 500a

5 To a solution of amine 2 (2.0 g, 2.7 mmol) in Hunig's base (5 mL) was added *N*-[2-bromoethyl]-phthalimide (0.76 g, 3 mmol). The mixture was heated to 100 °C in a sealed tube for 1.5h. The mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (K_2CO_3), filtered, and concentrated. The crude product was purified by silica gel chromatography (eluted with 1-4% methanolic ammonia (2M

10 NH_3) in CH_2Cl_2) to give the phthalimide derivative as a white solid (1.8 g, 1.9 mmol).

To a solution of this phthalimide (1.0 g, 1.1 mmol) in EtOH (10 mL) was added hydrazine (1 mL of 80% aqueous solution). The mixture was stirred at rt for 8h, then the solidified reaction residue was dissolved in CH_2Cl_2 (100 mL) and washed with water (3 x 50 mL). The organic layer was dried over K_2CO_3 , filtered and concentrated to give 0.82g of a white

15 solid which was used without further purification.

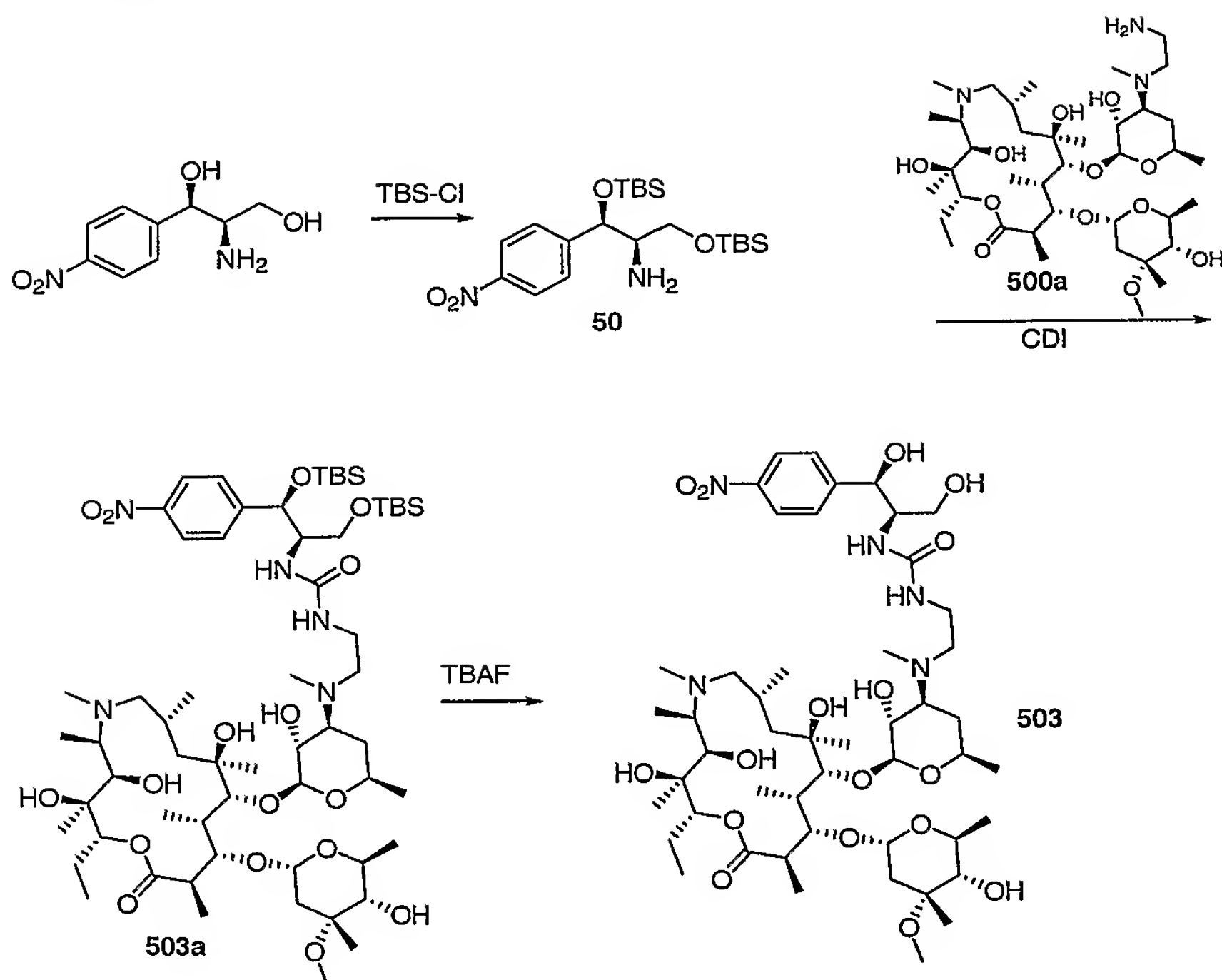
Synthesis of amine 500b

Compound 500b was synthesized from amine 2 *N*-[3-bromopropyl]-phthalimide using the conditions described above for compound 500a.

Compound 503 was synthesized from the amine 500a and the *N*-acyl imidazole derivative of the bis silyl ether derivative of D-(−)-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol. This yielded the bis-silyl-protected precursor 503a which was desilylated with tetrabutyl ammonium fluoride to afford compound 503 as shown in Scheme 121 below.

20

Scheme 121



Synthesis of compound 503

- 5 A solution of D-(-)-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol (2.1 g, 10 mmol) in dimethylformamide (200 mL) was treated with imadazole (2.0 g, 30 mmol) and *tert*-butyldimethylchlorosilane (3.0 g, 20 mmol), and stirred at 23 °C for 16 h. The reaction mixture was diluted with ethyl ether (300 mL), washed with H₂O (3 × 300 mL), and dried (Na₂SO₄). Flash chromatography (SiO₂, 20% ethyl acetate/hexanes) provided the *bis*-silyl ether **50** (2.6 g, 5.9 mmol) as a yellow oil.

- 10 A solution of the *bis*-silyl ether **50** (44 mg, 0.10 mmol) in dichloromethane (1.0 mL) was treated with triethylamine (0.028 mL, 0.20 mmol) and 1,1-carbonyldiimidazole (16 mg, 0.10 mmol), and stirred at 23 °C for 3 h. Amine **500a** (78 mg, 0.10 mmol) was added and the reaction mixture was stirred at 23 °C for an additional 12 h, and then evaporated to a yellow film and
- 15 purified by preparative thin-layer chromatography (SiO₂, 10% 2M NH₃-methanol/dichloromethane) to provide **503a** (65 mg, 0.064 mmol) as a white film: LCMS (ESI) *m/e* 623 (M+2H)²⁺

A solution of **503a** (50 mg, 0.040 mmol) in tetrahydrofuran (0.8 mL) was treated with tetrabutylammonium fluoride (0.16 mL of a 1.0 M solution, 0.16 mmol) and acetic acid (0.005 mL,

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0.08 mmol), and stirred at 23 °C for 4 h. The reaction mixture was diluted with H₂O (20 mL), and extracted with dichloromethane (3 × 20 mL), dried (Na₂SO₄), evaporated, and purified by preparative thin-layer chromatography (SiO₂, 5% 2M NH₃-methanol/dichloromethane) to provide **503** (19 mg, 0.019 mmol) as a white film: LCMS (ESI) *m/e* 509 (M+2H)²⁺.

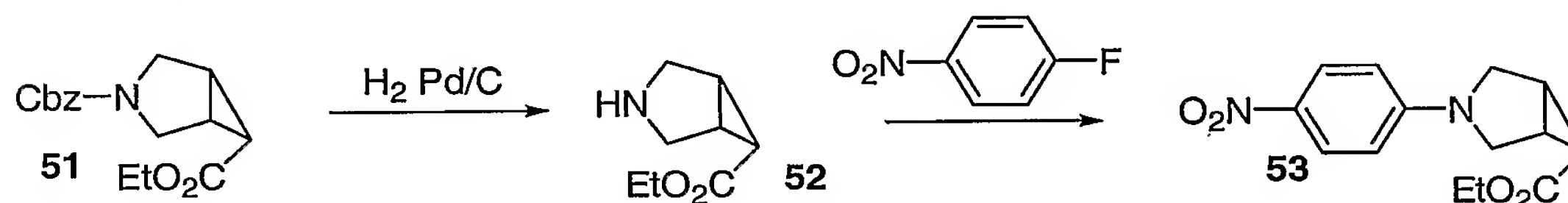
5

Synthesis of compound 502

Compound **502** was synthesized from amine **500b** and D-(-)-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol as described above for compound **503**.

10 Synthesis of compound 501

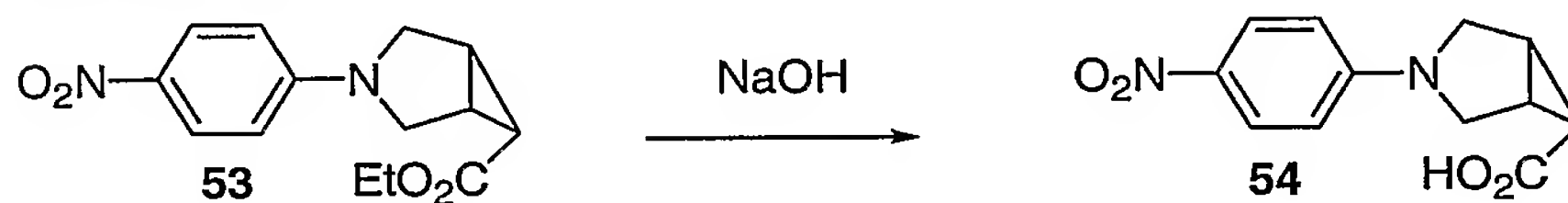
Scheme 122



A solution of CBZ amine **51** (US Patent No. 5,164,402) (1.5 g, 5.2 mmol) in methanol (30 mL) was treated with 10% Pd/C (0.15 g) and stirred under a balloon of hydrogen at 23 °C for 2 h. The reaction mixture was filtered through a plug of silica gel and evaporated to provide the crude amine **52** as a yellow oil.

A solution of this amine **52** in acetonitrile (5.0 mL) was treated with diisopropylethylamine (2.0 mL, 12 mmol) and 4-fluoro-nitrobenzene (0.60 mL 5.7 mmol), and stirred at 70 °C for 16 h. The reaction mixture was evaporated and purified by flash chromatography (SiO₂, 20–50% ethyl acetate/hexanes) to provide the ethyl ester **53** (0.76 g, 2.8 mmol) as a yellow oil.

Scheme 123



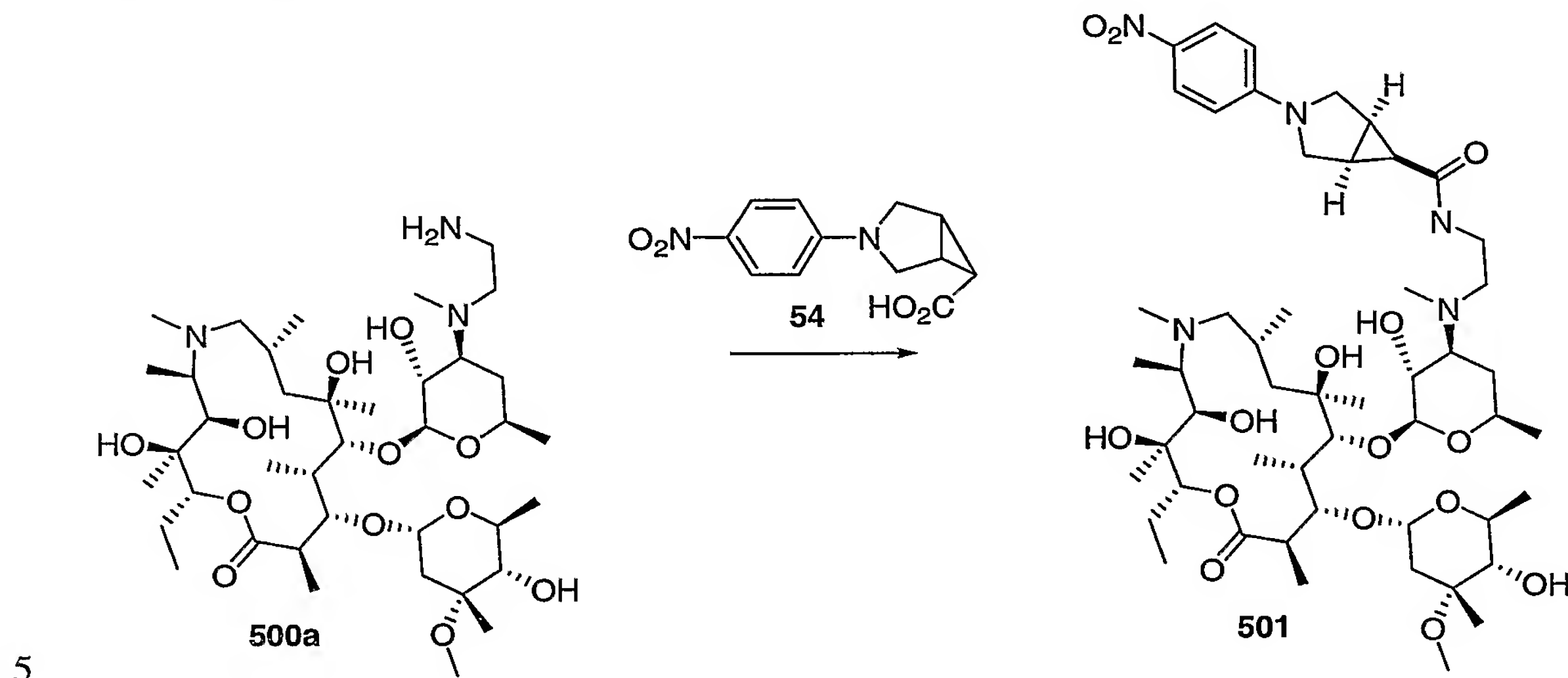
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A solution of ethyl ester **53** (0.43 g, 1.6 mmol) in tetrahydrofuran (12 mL) and methanol (4.0 mL) was treated with 1.0 M aqueous sodium hydroxide (3.1 mL, 3.1 mmol) and stirred at 50 °C for 6 h. The reaction mixture was cooled to room temperature and quenched by the addition

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of 1.0 M hydrochloric acid (3.1 mL, 3.1 mmol), extracted with dichloromethane (3×20 mL), dried (Na_2SO_4), and evaporated to provide the carboxylic acid **54** (0.32 g, 1.1 mmol) as a yellow powder.

Scheme 124



A solution of amine **500a** (78 mg, 0.10 mmol) in dichloromethane (1.0 mL) was treated with carboxylic acid **54** (25 mg, 0.10 mmol), triethylamine (0.042 mL, 0.3 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (57 mg, 0.15 mmol) and stirred at 23 °C for 4 h. The reaction mixture was evaporated to a yellow film and purified by preparative thin-layer chromatography (SiO_2 , 5% 2M NH_3 -methanol/dichloromethane) to provide **501** (20 mg, 0.02 mmol) as a yellow film: LCMS (ESI) m/e 505 ($\text{M}+2\text{H}$) $^{2+}$.

10

Synthesis of compounds **504**, **505**, **507**, **508**, and **512** -**515**

These compounds were synthesized from amines **500a** and **500b** and the appropriate carboxylic acids using protocols analogous to the one described above for compound **501**.

15

Synthesis of compound **506**

To a solution of **500a** (50 mg, 0.056 mmol) in CH_2Cl_2 (1 mL) and Hunig's base (0.1 mL) was added 8-quinoline sulfonyl chloride (0.07 mmol). The mixture was stirred at rt for 1h, then the entire reaction mixture was placed directly on a silica gel column and eluted with 0-3% 2M methanolic ammonia in CH_2Cl_2 to afford the **506** as a white solid (52 mg, 0.052 mmol). LCMS (ESI) m/e 535 ($\text{M}+2\text{H}$) $^{2+}$.

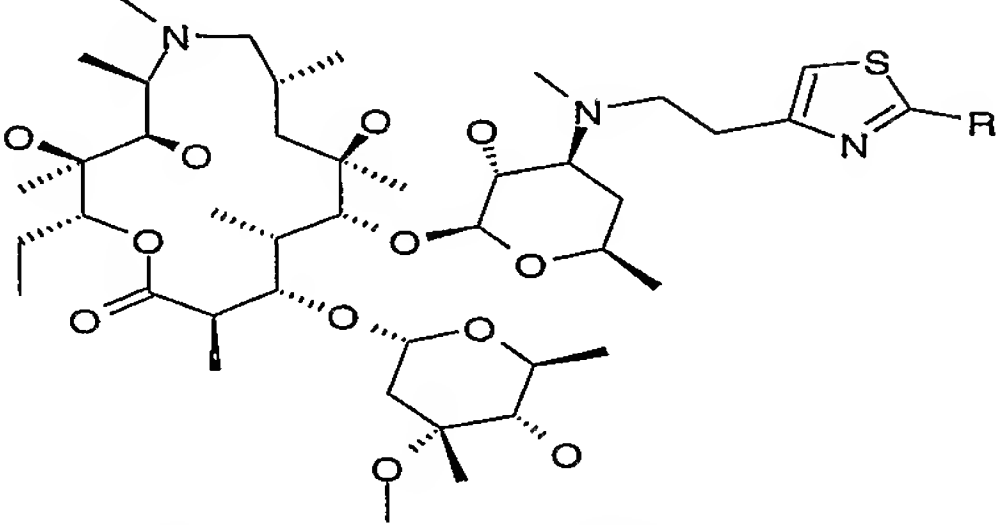
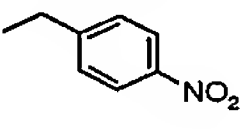
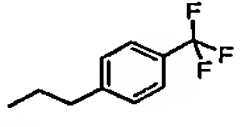
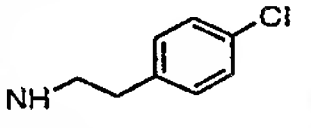
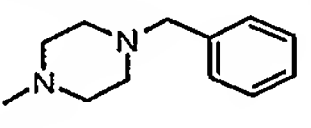
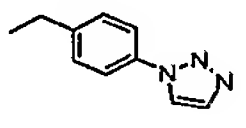
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Synthesis of compounds 509, 510 and 511.

Compound **509**, **510** and **511** were synthesized from amines **500a** and **500b** in a similar fashion to the compound **506**.

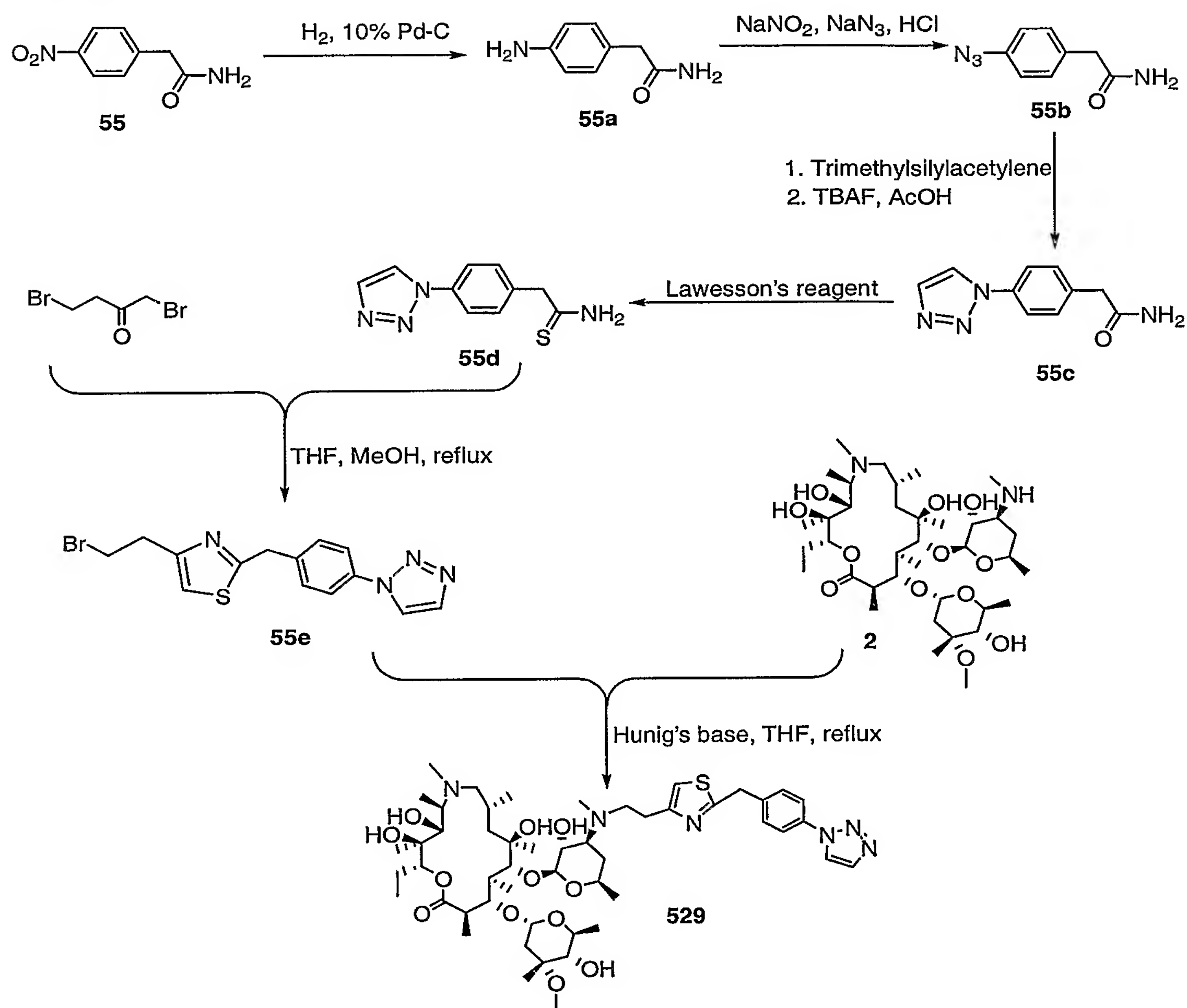
5 Example 8 Synthesis of compounds 525-529**Table 9**

		
Compound	R	LCMS (M/Z)
525		491.6 (M + 2H) ²⁺ 981.7 (M + H) ⁺ 1003.8 (M + Na) ⁺
526		510.0 (M + 2H) ²⁺ 1018.8 (M + H) ⁺ 1040.7 (M + Na) ⁺
527		494.2 (M + 2H) ²⁺ 985.8 (M + H) ⁺
528		511.1 (M + 2H) ²⁺ 1020.9 (M + H) ⁺
529		502.5 (M + 2H) ²⁺ 1003.4 (M + H) ⁺

The thiazole linked compounds of Table 9 were synthesized by alkylation of 3'-N-desmethyl azithromycin **2** with 4-[2-bromoethyl] thiazoles as shown in Scheme 125 and as demonstrated below for the synthesis of compound **529**.

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Scheme 125



Synthesis of 4-aminophenylacetamide 55a

- 5 To a solution of 4-nitrophenylacetamide **55** (3.2 g, 1.78 mmol) in methanol (50 mL) was added 10% Pd-C (0.32 g) and the resulted mixture was stirred at room temperature for 24 h under 1 atm hydrogen atmosphere. Pd-C was removed by filtration on Celite. The filtered solution was evaporated to provide **55a** (2.35 g, 90% yield). ^1H NMR (300 MHz, CDCl_3 - CD_3OD): δ 7.06 (d, J = 8 Hz, 2H), 6.72 (d, J = 8 Hz, 2H), 3.41 (s, 2H).

10

Synthesis of azide 55b

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Azide **55b** was prepared from **55a** following the procedure for the preparation of azide **14au**. Yield, 44%; ¹HNMR (300 MHz, CDCl₃-CD₃OD): δ 7.20 (d, *J* = 6 Hz, 2H), 6.94 (d, *J* = 6 Hz, 2H), 3.45 (s, 2H).

5 Synthesis of triazole **55c**

A solution of azide **55b** (640 mg, 3.64 mmol) and trimethylacetylene (700 mg, 7.14 mmol) in DMF (25 mL) was heated at 90 °C for 48 h. The reaction was evaporated to dry in vacuum. The resulted residue was dissolved in THF (15 mL). A solution of TBAF (1.0 M in THF, 7.5 mL, 7.5 mmol) and acetic acid (220 mg, 3.6 mmol) was added. The reaction was stirred at RT for 24 h. THF was removed and the residue was suspended in water and stirred for 15 min. a white solid was collected by filtration to provide **55c** (596 mg, 81 % yield). ¹HNMR (300 MHz, CDCl₃-CD₃OD): δ 8.01 (d, *J* = 1 Hz, 1H), 7.69 (d, *J* = 1 Hz, 1H), 7.57 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 8 Hz, 2H), 3.45 (s, 2H).

15 Synthesis of thiocarboxylic amide **55d**

The mixture of **55c** (180 mg, 0.89 mmol) and Lawesson's reagent (288 mg, 0.71 mmol) in THF (3 mL) was refluxed under argon for 2 h. The reaction was diluted with CH₂Cl₂, washed with brine, dried over MgSO₄ and concentrated in vacuum. Chromatography (25:1:0.1/CH₂Cl₂:MeOH:NH₃·H₂O) of crude product afforded **55d** (150 mg, 77 % yield). ¹HNMR (300 MHz, CDCl₃-CD₃OD): δ 8.01 (s, 1H), 7.75 (s, 1H), 7.62 (d, *J* = 8 Hz, 2H), 7.44 (d, *J* = 8 Hz, 2H), 3.96 (s, 2H).

Synthesis of thiazole **55e**

To a solution of **55d** (165 mg, 0.72 mmol) in THF (8 mL) and MeOH (2 mL) was added 1,4 dibromobutanone (130 mg, 0.60 mmol). After refluxing for 2 h, the reaction was diluted with CH₂Cl₂, washed with saturated NaHCO₃, dried over MgSO₄ and concentrated. Chromatography (40:1:0.1/CH₂Cl₂:MeOH:NH₃·H₂O) of crude product provided **55e** (165 mg, 79 % yield); ¹HNMR (300 MHz, CDCl₃-CD₃OD): δ 7.92 (d, *J* = 1 Hz, 1H), 7.76 (d, *J* = 1 Hz, 1H), 7.64 (d, *J* = 9 Hz, 2H), 7.39 (d, *J* = 9 Hz, 2H), 6.87 (s, 1H), 4.29 (s, 2H), 3.63 (t, *J* = 7 Hz, 2H), 3.22 (t, *J* = 7 Hz, 2H).

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Synthesis of 529

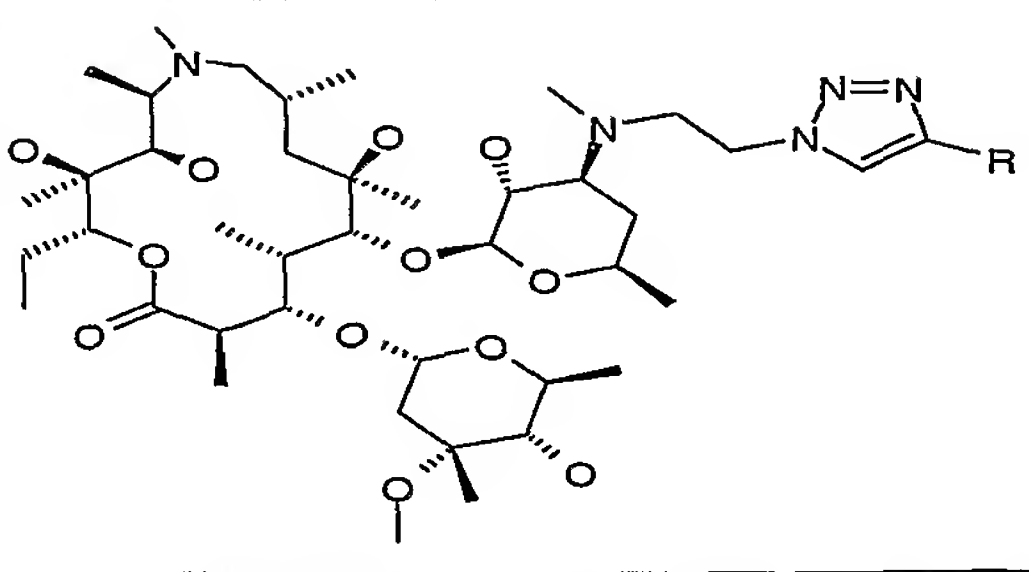
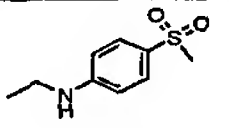
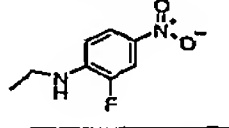
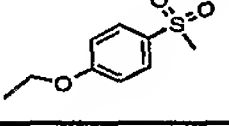
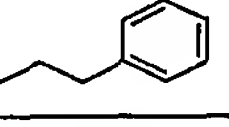
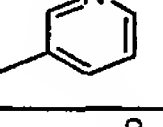
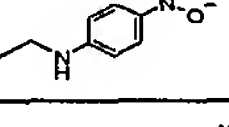
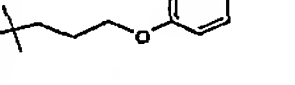
The mixture of **55e** (150 mg, 0.43 mmol), N-desmethylazithromycin **2** (276 mg, 0.36 mmol), Hunig's base (4 mL) and KI (300 mg, 1.81 mmol) in THF (10 mL) was refluxed for 8 h. THF was removed in vacuum and the residue was dissolved in CH₂Cl₂. the solution was washed
5 with brine, dried over MgSO₄, concentrated to dry and purified by chromatography (25:1:0.1/CH₂Cl₂:MeOH:NH₃:H₂O) to provide **529** (255 mg, 71 % yield); MS (ESI): 1003.4 (M + H)⁺, 502.5 (100%). ¹HNMR (300 MHz, CDCl₃, partial) δ 7.92 (s, 1H), 7.78 (s, 1H), 7.64 (d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 8 Hz, 2H), 6.78 (s, 1H), 4.38 (d, *J* = 7 Hz, 1H), 4.29 (s, 2H), 3.26 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H).

10

The remaining compounds of Table 9 were synthesized by alkylating 3'-N-desmethyl azithromycin **2** with appropriately substituted 4-[2-bromoethyl] thiazoles using procedures analogous to those presented above for compound **529**.

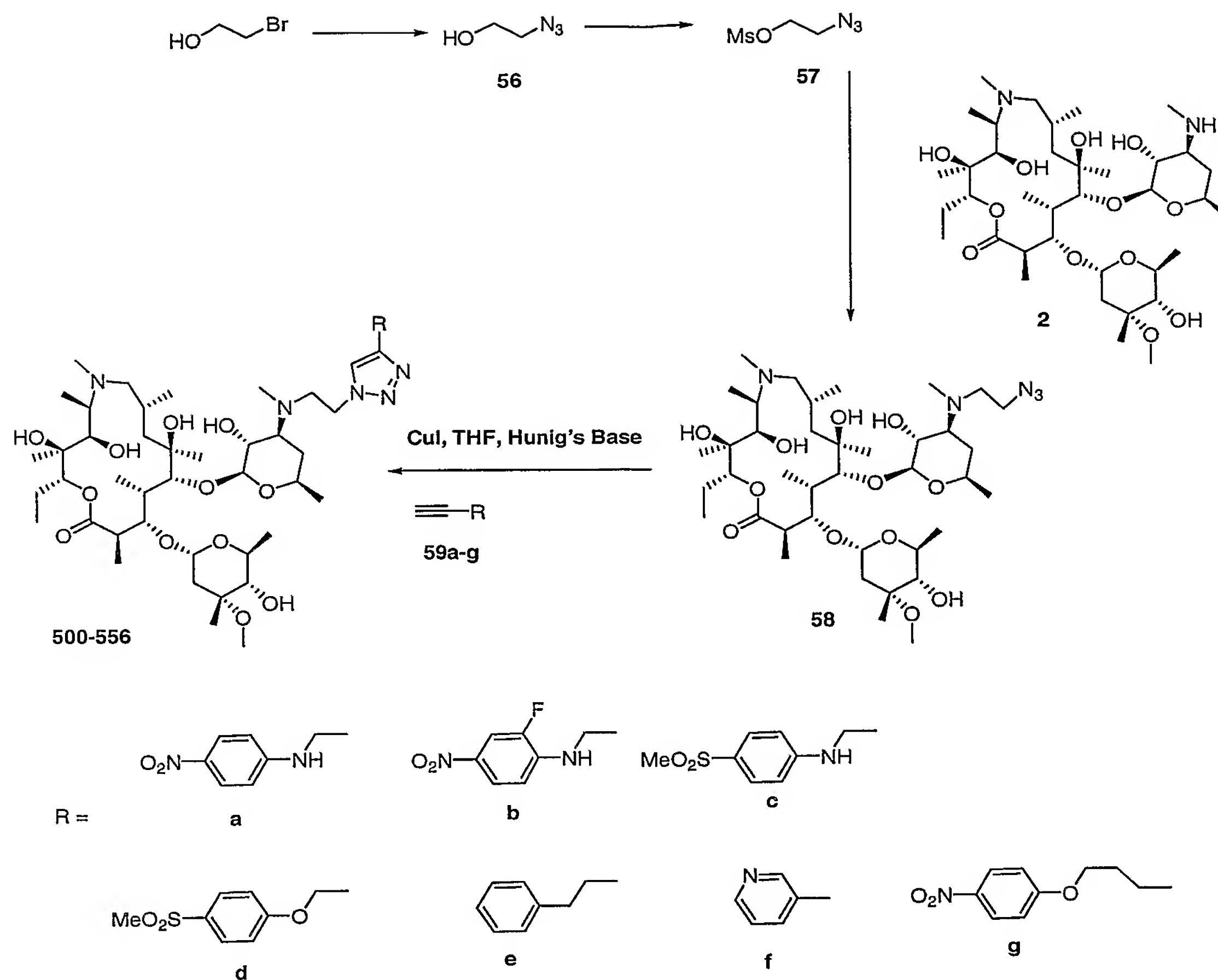
Example 9 Synthesis of compounds 550-556

Table 10

		
Compound	R	LCMS (M/Z)
550		507 (M + 2H) ²⁺ 1014 (M + H) ⁺
551		500 (M + 2H) ²⁺ 999 (M + H) ⁺
552		508 (M + 2H) ²⁺ 1015 (M + H) ⁺
553		468 (M + 2H) ²⁺ 935 (M + H) ⁺
554		455 (M + 2H) ²⁺ 908 (M + H) ⁺
555		491 (M + 2H) ²⁺ 981 (M + H) ⁺
556		505.5 (M + 2H) ²⁺ 1010.4 (M + H) ⁺

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Scheme 126

**Synthesis of 2-azido ethanol (56):**

5 A mixture of 2-bromoethanol (2 mL, 26.8 mmol) and NaN_3 (3.48 g, 53.6 mmol) was heated at 70°C for 12h and then poured into a mixture of ethyl ether and water (150 mL, 1:1). The organic layer was separated and the aqueous layer was extracted with ethyl ether (2 x 30 mL). The combined organic layer was washed with water (1 x 100 mL), dried and carefully reduced the volume and used for the next step without further purification.

10

Synthesis of 2-azido ethyl methylsulphonate (57):

Methane sulphonyl chloride (3.1 mL, 40.2 mmol) was added to a solution of 2 (26.8 mmol) and triethyl amine (5.6 mmol, 40.2 mmol) in methylene chloride (50 mL) at 0°C and stirred at ambient temperature for 12h. The reaction mixture was diluted with methylene chloride (50 mL) and washed with saturated sodium bicarbonate (2 x 100 mL) solution. The solution was

15

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dried with anhydrous Na₂SO₄, filtered and carefully concentrated to reduced volume and used for the next step without further purification.

Synthesis of 58:

5 A solution of amine **2** (2 g, 2.7 mmol) and **57** (8.2 mmol) in a mixture of THF and Hunig's base (40 mL, 1:1) was refluxed for 24h. The reaction mixture was concentrated and dissolved in CH₂Cl₂ (100 mL). The organic layer was washed with brine (2 x 100 mL), dried, concentrated in reduced pressure and purified by flash chromatography over silica gel (CH₂Cl₂ : 2% NH₃-MeOH) to afford 1 g of **58**. MS (ESI) *m/e* 805 (M+H)⁺,

10

Synthesis of 59a-c, 59d and 59g:

Alkynes **59a-c** were synthesized according to the procedure described in literature (*J. Med. Chem.*, **1996**, 39, 904-917).

15 Data for **59a**: ¹H NMR (300 MHz, CDCl₃): δ 2.29 (t, 1H), 4.04 (dd, 2H), 4.68 (brs, 1H), 6.65 (d, 2H), 8.14 (d, 2H).

Data for **59b**: ¹H NMR (300 MHz, CDCl₃): δ 2.32 (t, 1H), 4.09 (dd, 2H), 4.90 (brs, 1H), 6.79 (t, 1H), 7.93 (dd, 1H), 8.06 (dd, 1H).

20

Data for **59c**: ¹H NMR (300 MHz, CDCl₃): δ 2.27 (t, 1H), 3.02 (s, 3H), 4.01 (dd, 2H), 4.53 (brs, 1H), 6.73 (d, 2H), 7.75 (d, 2H).

Alkyne **59d** was synthesized by alkylation of 4-methylsulphonyl phenol with propargyl bromide in presence of K₂CO₃. ¹H NMR (300 MHz, CDCl₃): δ 2.58 (t, 1H), 3.04 (s, 3H), 4.78 (d, 2H), 7.11 (d, 2H), 7.89 (d, 2H).

25

Alkyne **59g**: To a solution of 4-Nitrophenol (1g, 7.2 mmol), 4-pentyne -1-ol (0.775 mL, 7.9 mmol) and Ph₃P (2.2 g, 8.28 mmol) in THF (15 mL) was added DIAD (2 mL, 7.9 mmol) at 0°C and stirred 2h at ambient temperature. The solution was concentrated and the residue was redissolved in diethyl ether (75 mL). The ethereal layer was successively washed with brine (1 x 50 mL), 1N NaOH (1 x 50 mL) and H₂O (1 x 50 mL). The resulting solution was dried (anhydrous Na₂SO₄), concentrated and the crude material was purified by flash chromatography

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over silica gel (20 % EtOAc-hexane). After titration with ether, 1g of **59g** was isolated as an off-white solid. ^1H NMR (300 MHz, CDCl_3): δ 1.99 (t, 1H), 2.03-2.09 (m, 2H), 2.44 (dt, 2H), 4.18 (t, 2H), 6.97 (d, 2H), 8.22 (d, 2H).

5 Synthesis of 550-556:

General Method:

To a mixture of **59a-g** (0.0746 mmol), **58** (0.0622 mmol) and CuI (0.0746 mmol) was added THF (5 mL) under argon atmosphere. Then was added few drops of Hunig's base and stirred at ambient temperature for 2h. The reaction mixture was quenched with saturated NH_4OH solution containing 20% NH_4OH (25 mL) and stirred for 30 mins at ambient temperature. The mixture was extracted with methylene chloride (3 x 50 mL) and the combined organic extract was washed with saturated ammonium chloride solution containing 10% ammonium hydroxide (2 x 50 mL). The resulting solution was dried with anhydrous Na_2SO_4 , concentrated and purified by preparative TLC (first using CH_2Cl_2 : 2 % NH_3 -MeOH = 10:1 and then EtOAc: Et_3N = 8:2) to afford pure **550-556**.

Data for **555**: Yield 50%. MS (ESI) m/e 981 ($\text{M}+\text{H}$) $^+$, 491 ($\text{M}+2\text{H}$) $^+$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 0.86-0.91 (m, 6H), 0.94 (d, 2H), 3.21 (t, 1H), 3.3 (s, 3H), 4.05 (t, 1H), 4.26 (brs, 1H), 4.36 (d, 1H), 4.44 (t, 2H), 4.51 (d, 2H), 4.68 (d, 2H), 5.12 (d, 2H), 5.2 (brs, 1H), 6.61 (d, 2H), 7.67 (s, 1H), 8.14 (d, 2H).

Data for **551**: Yield 60%. MS (ESI) m/e 999 ($\text{M}+\text{H}$) $^+$, 500 ($\text{M}+2\text{H}$) $^+$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 0.86-0.90 (m, 6H), 0.91 (d, 3H), 3.29 (s, 3H), 4.57 (d, 2H), 5.15 (d, 1H), 5.30 (brs, 1H), 6.76 (t, 1H), 7.70 (s, 1H), 7.89 (dd, 1H), 7.99 (dd, 1H).

25

Data for **550**: Yield 50%. MS (ESI) m/e 1014 ($\text{M}+\text{H}$) $^+$, 507 ($\text{M}+2\text{H}$) $^+$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 0.87 (d, 3H), 0.91 (d, 3H), 1.09 (d, 3H), 3.32 (s, 3H), 3.61 (d, 1H), 4.66 (d, 1H), 4.99 (t, 1H), 5.11 (d, 1H), 6.68 (d, 2H), 7.63 (s, 1H), 7.70 (d, 2H).

Data for **552**: Yield 55%. MS (ESI) m/e 1015 ($\text{M}+\text{H}$) $^+$, 508 ($\text{M}+2\text{H}$) $^+$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 0.86-0.91 (m, 6H), 0.99 (d, 3H), 3.28 (s, 3H), 3.64 (d, 1H), 3.67 (s, 1H), 4.05

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(m, 1H), 4.25 (d, 1H), 4.38 (d, 1H), 4.45 (t, 1H), 4.70 (d, 1H), 5.11 (d, 1H), 5.27 (s, 2H), 7.12 (d, 2H), 7.81 (s, 1H), 7.86 (d, 2H).

5 Data for **553**: Yield 50%. MS (ESI) *m/e* 935 (M+H)⁺, 468 (M+2H)⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ 0.86-0.92 (m, 6H), 0.99 (d, 3H), 3.48 (s, 3H), 3.62 (d, 1H), 3.66 (s, 1H), 4.02-4.07 (m, 1H), 4.35-4.41 (m, 3H), 4.67 (dd, 1H), 5.09 (d, 1H), 7.17-7.31 (m, 6H).

10 Data for **554**: Yield 40%. MS (ESI) *m/e* 908 (M+H)⁺, 455 (M+2H)⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ 0.86-0.91 (m, 6H), 0.97 (d, 3H), 3.25 (s, 3H), 3.62 (d, 1H), 3.66 (s, 1H), 4.05 (brt, 1H), 4.23 (brs, 1H), 4.38 (d, 1H), 4.50 (t, 2H), 4.67 (d, 1H), 5.11 (d, 1H), 7.35 (dd, 1H), 8.17 (s, 1H), 8.20 (d, 1H), 8.56 (d, 1H), 8.98 (s, 1H).

Data for **556**: Yield 90%. MS (ESI) *m/e* 1010 (M+H)⁺, 505.5 (M+2H)⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ 0.86-0.91 (m, 6H), 0.94 (d, 3H), 3.30 (s, 3H), 4.12 (t, 2H), 4.26 (t, 2H), 4.27-4.42 (m, 3H), 4.67 (dd, 1H), 5.05 (d, 1H), 6.96 (d, 2H), 7.42 (s, 1H), 8.20 (d, 2H).

15 **Synthesis of azides 14a-14gm**

The azides **14a-14gm** shown in Table 11 were used to synthesize numerous compounds of the invention including **101-280**, **301-357**, **401-417**, **425-451**, and **460-466**. The azides were readily synthesized by methods known from the literature. Exemplary azide syntheses are presented below. The remaining azides of Table 11 were synthesized in analogous fashion from
20 appropriate commercial starting materials.

Table 11

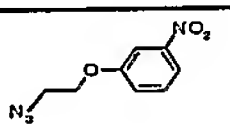
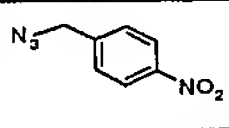
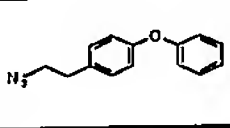
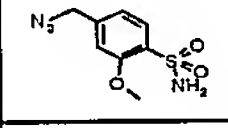
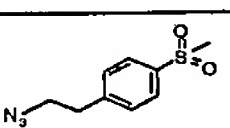
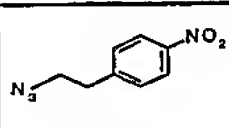
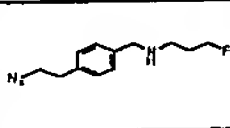
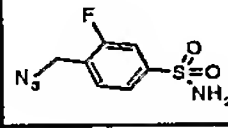
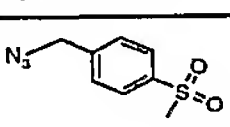
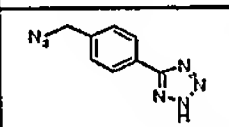
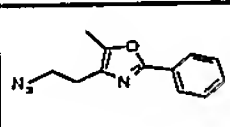
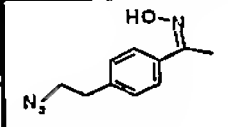
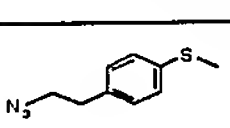
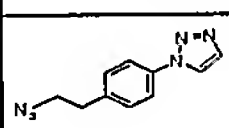
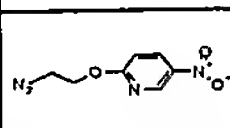
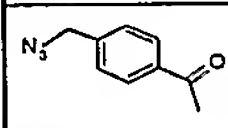
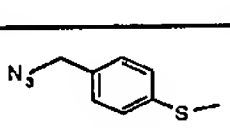
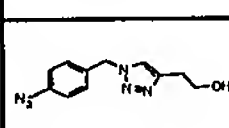
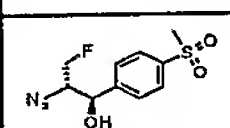
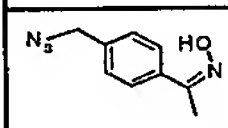
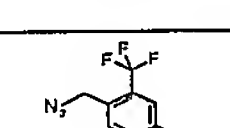
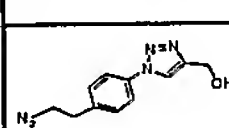
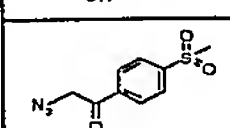
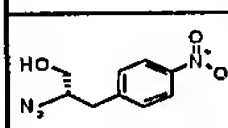
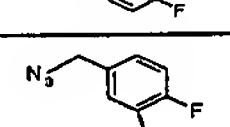
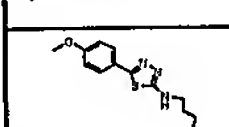
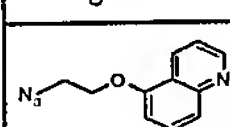
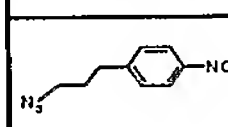
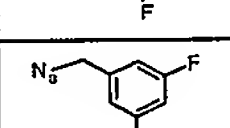
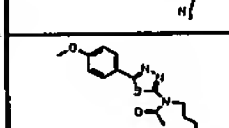
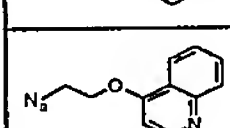
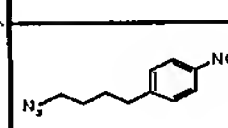
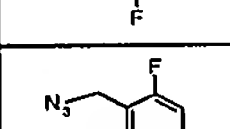
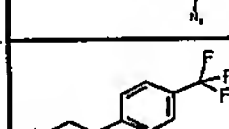
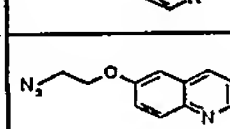
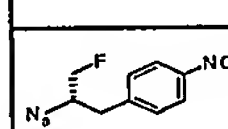
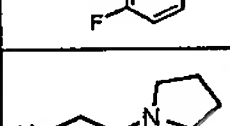
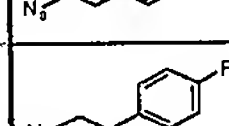
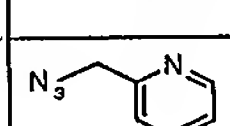
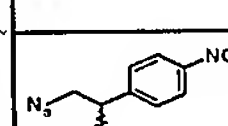
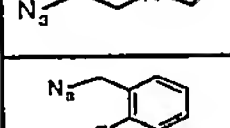
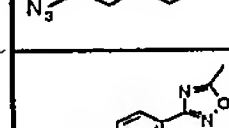
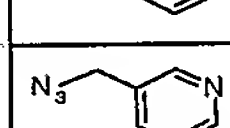
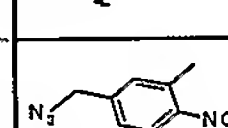
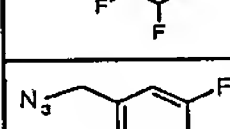
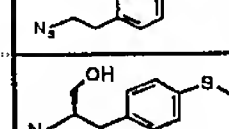
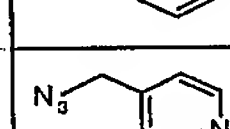
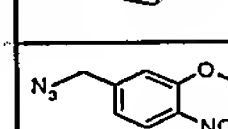
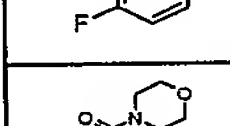
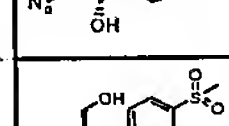
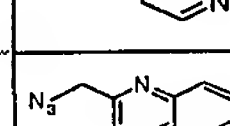
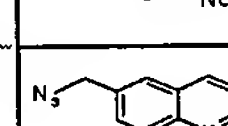
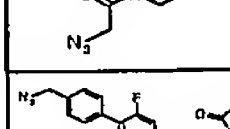
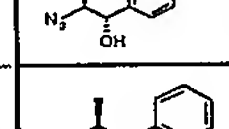
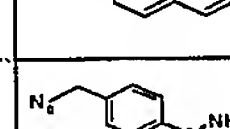
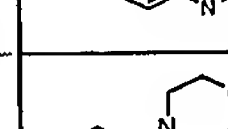
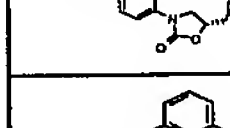
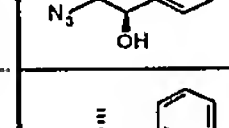
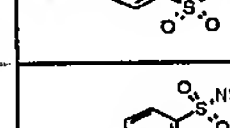
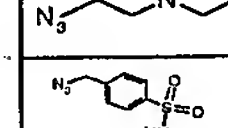
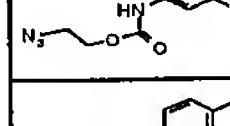
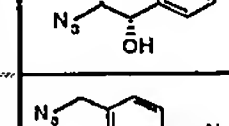
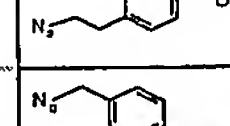
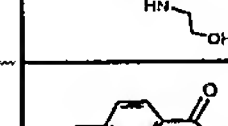
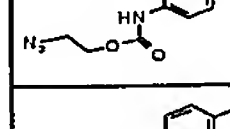
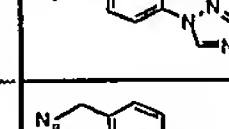
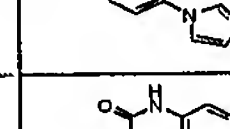
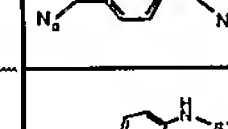
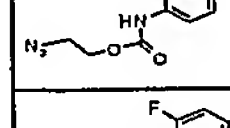
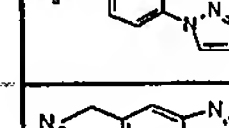
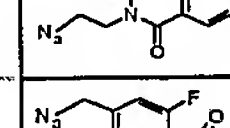
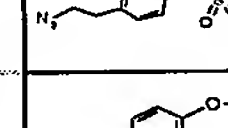
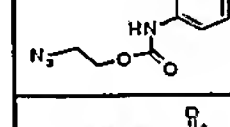
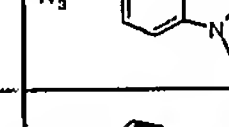
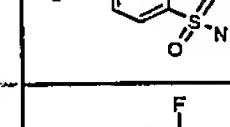
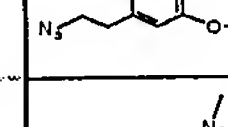
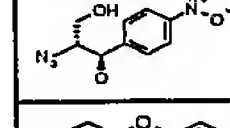
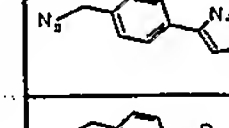
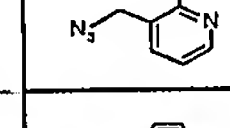
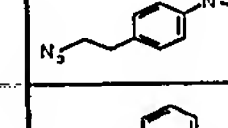
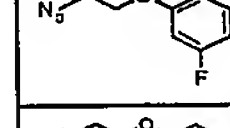
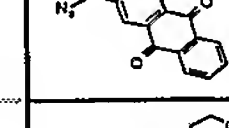
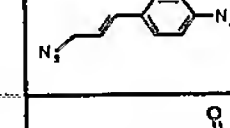
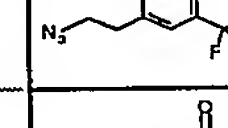
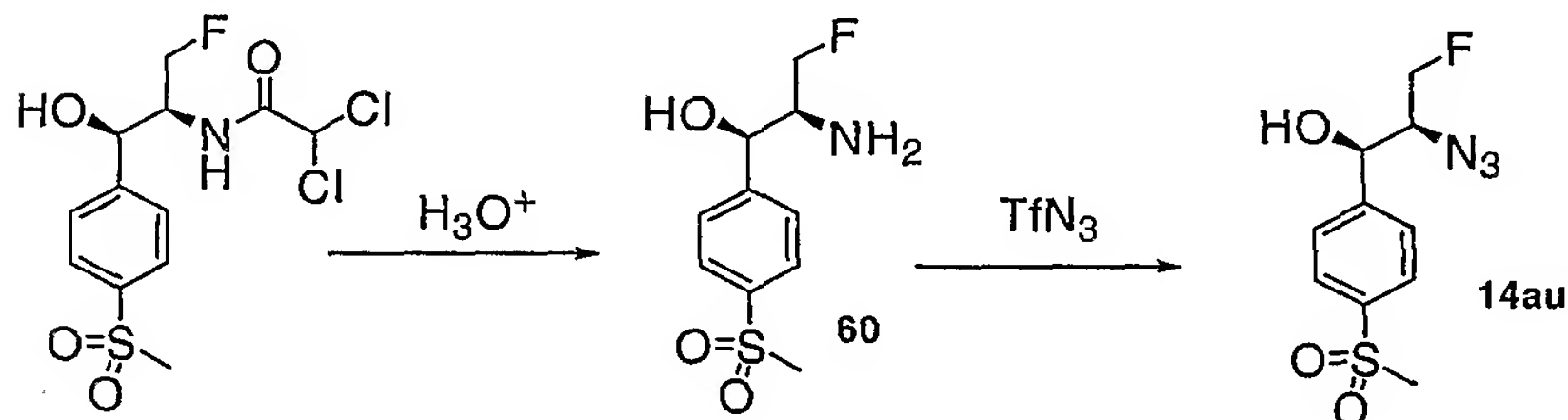
Structure	Compound	Structure	Compound	Structure	Compound	Structure	Compound
	14a		14v		14aq		14bl
	14b		14w		14ar		14bm
	14c		14x		14as		14bn
	14d		14y		14at		14bo
	14e		14z		14au		14bp
	14f		14aa		14av		14bq
	14g		14ab		14aw		14br
	14h		14ac		14ax		14bs
	14i		14ad		14ay		14bt
	14j		14ae		14az		14bu
	14k		14af		14ba		14bv
	14l		14ag		14bb		14bw
	14m		14ah		14bc		14bx
	14n		14ai		14bd		14by
	14o		14aj		14be		14bz
	14p		14ak		14bf		14ca
	14q		14al		14bg		14cb
	14r		14am		14bh		14cc
	14s		14an		14bi		14cd
	14t		14ao		14bj		14ce
	14u		14ap		14bk		14cf

TABLE 11 continued

Structure	Compound	Structure	Compound	Structure	Compound	Structure	Compound
	14cg		14dd		14dy		14ev
	14ch		14de		14dz		14ew
	14ci		14df		14ea		14ex
	14cj		14dg		14eb		14ey
	14ck		14dh		14ec		14ez
	14cl		14di		14ed		14fa
	14cm		14dj		14ef		14fb
	14cn		14dk		14eg		14fc
	14co		14dl		14eh		14fd
	14cp		14dm		14ei		14fe
	14cq		14dn		14ej		14ff
	14cr		14do		14el		14fg
	14cs		14dp		14em		14fh
	14ct		14dq		14en		14fi
	14cu		14dr		14eo		14fj
	14cv		14ds		14ep		14fk
	14cx		14dt		14eq		14fl
	14cy		14du		14er		14fm
	14da		14dv		14es		14fn
	14db		14dw		14et		14fo
	14dc		14dx		14eu		14fp

TABLE 11 continued

Structure	Compound	Structure	Compound	Structure	Compound	Structure	Compound
	14fq		14fw		14gc		14gi
	14fr		14fx		14gd		14gj
	14fs		14fy		14ge		14gk
	14ft		14fz		14gf		14gl
	14fu		14ga		14gg		14gm
	14fv		14gb		14gh		

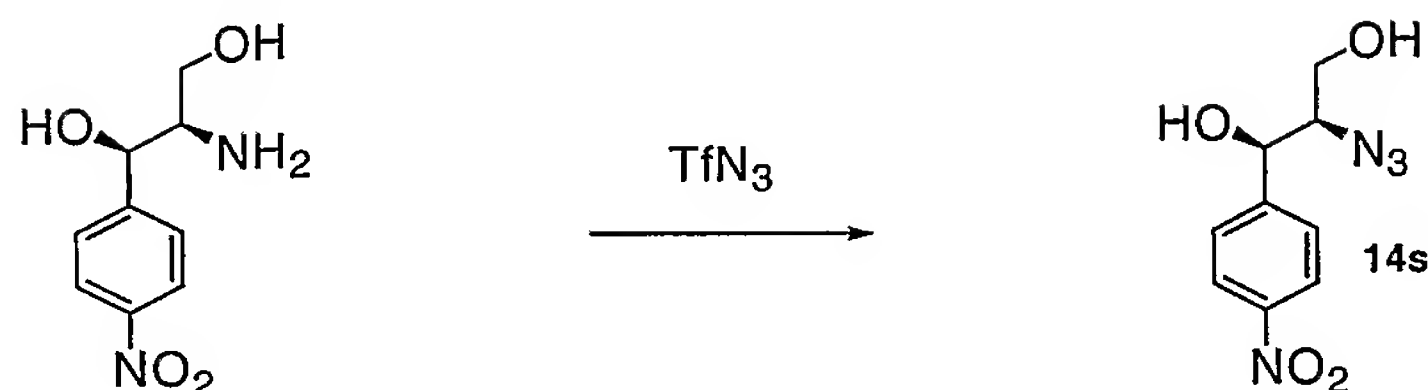
5 Scheme 127. Synthesis of azide **14au**Synthesis of **14au**

10 A solution of florfenicol (0.090 g, 0.25 mmol) in acetic acid (3.0 mL) was treated with sulfuric acid (10%, 15 mL) and heated to 110 °C for 12 h. The reaction mixture was cooled to room temperature, treated with 10 M aqueous sodium hydroxide to adjust the pH to 14, extracted with dichloromethane (3 × 30 mL), dried (Na₂SO₄), and evaporated to provide florfenicol amine **60** (65 mg, 0.25 mmol) as a yellow oil.

15 A solution of florfenicol amine **60** (0.90 g, 3.6 mmol) in H₂O (10 mL) and methanol (30 mL) was treated with triethylamine (1.5 mL, 10.8 mmol) and trifluoromethanesulfonyl azide (13.4 mmol dissolved in 20 mL of dichloromethane; solution prepared according to method described in *J. Am. Chem. Soc.* **2002**, *124*, 10773), and stirred at 0 °C 3 h and then warmed to 23 °C for 1 h. The reaction mixture was diluted with H₂O (30 mL), extracted with dichloromethane (30 mL) and evaporated. Flash chromatography (SiO₂, 50–100% ethyl acetate/hexanes) provided azide **14au** (0.65 g, 2.4 mmol) as a yellow solid.

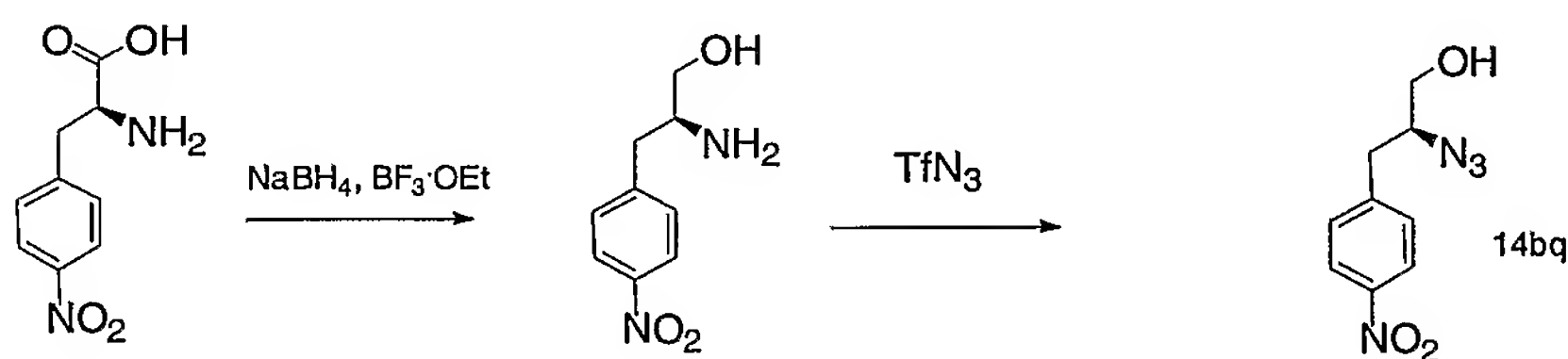
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Scheme 128. Synthesis of azide **14s****Synthesis of azide **14s****

5 A solution of D-(-)-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol (0.42 g, 2.0 mmol) in H_2O (5 mL) and methanol (17 mL) was treated with triethylamine (0.84 mL, 6.0 mmol) and trifluoromethanesulfonyl azide (3.0 mmol dissolved in 5 mL of dichloromethane; solution prepared according to method described in *J. Am. Chem. Soc.* **2002**, *124*, 10773), and stirred at 23 °C for 3 h. The reaction mixture was diluted with H_2O (30 mL), extracted with

10 dichloromethane (30 mL) and evaporated. Flash chromatography (SiO_2 , 50–100% ethyl acetate/hexanes) provided azide **14s** (0.28 g, 1.2 mmol) as a yellow solid.

Scheme 129. Synthesis of azide **14bq****Synthesis of azide **14bq****

15 To a stirred 0°C solution of 4-nitrophenylalanine (4.6g, 20 mmol) and NaBH_4 (3.2g, 84 mmol) in THF (50 mL) was added $\text{BF}_3 \cdot \text{OEt}$ (14.8 mL, 106 mmol). The reaction was warmed to rt and stirred for 24h. The mixture was cooled to 0°C and quenched with methanol. The reaction mixture was filtered and the filtrate concentrated to give a solid residue. 10% of this residue was

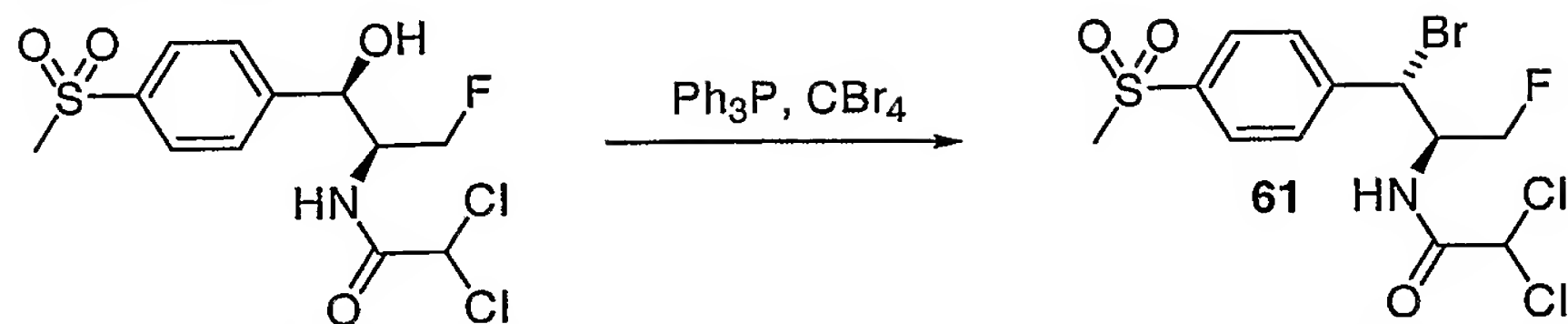
20 dissolved in water (5mL), methanol (20mL) and triethyl amine (0.9 mL). Triflic azide solution (3.5 mmol dissolved in 7 mL of dichloromethane; solution prepared according to method described in *J. Am. Chem. Soc.* **2002**, *124*, 10773) was added and the mixture was stirred at rt for 14h. The reaction mixture was diluted with dichloromethane (30mL) washed with saturated NaHCO_3 , and with brine. The organic extract was dried, filtered and concentrated to give **14bq**

25 as a white solid (150mg)

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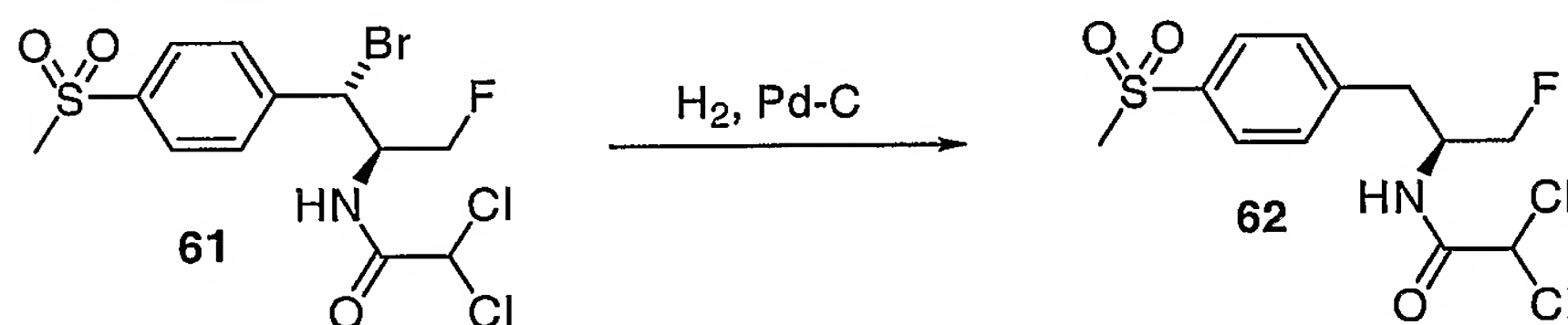
Synthesis of azide 14ed

Scheme 130



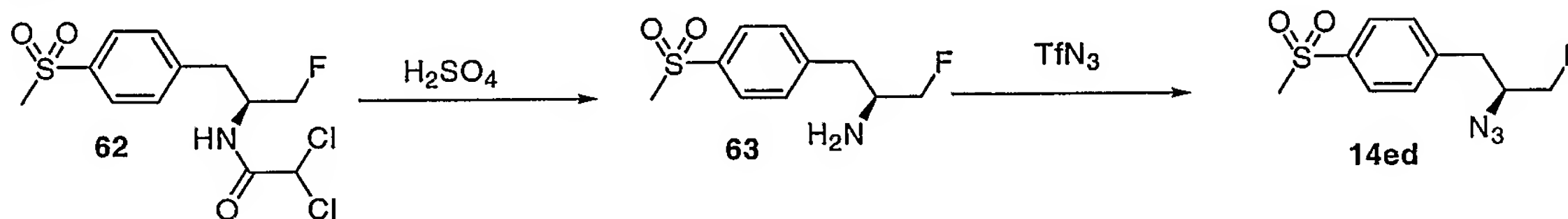
A solution of florfenicol (0.494 g, 1.38 mmol) in acetonitrile (15.0 mL) was treated with carbontetrabromide (0.594 g, 1.66 mmol) and triphenylphosphine (0.434 g, 1.66 mmol), and stirred at 23 °C for 12 h. The reaction mixture evaporated to a yellow residue and purified by flash chromatography (SiO₂, 10% ethyl acetate/dichloromethane) to provide **61** (0.28 g, 0.67 mmol) as a white powder.

10 Scheme 131



A solution of **61** (0.20 g, 0.41 mmol) in methanol (5.0 mL) was treated with 10% palladium on charcoal (20 mg) and stirred at 23 °C for 2 h under a balloon of hydrogen. The reaction mixture was filtered, evaporated and purified by preparative thin-layer chromatography (SiO₂, 10% ethyl acetate/dichloromethane) to afford **62** (90 mg, 0.26 mmol) as a white film.

Scheme 132



20

A solution of **62** (90 mg, 0.26 mmol) in acetic acid (3.0 mmol) was treated with 10% sulfuric acid (15 mL) and heated to 110 °C for 12 h. The reaction mixture was cooled to room temperature, treated with 10 M aqueous sodium hydroxide to adjust the pH to 14, extracted with dichloromethane (3 × 30 mL), dried (Na₂SO₄), and evaporated to provide crude **63** as a yellow

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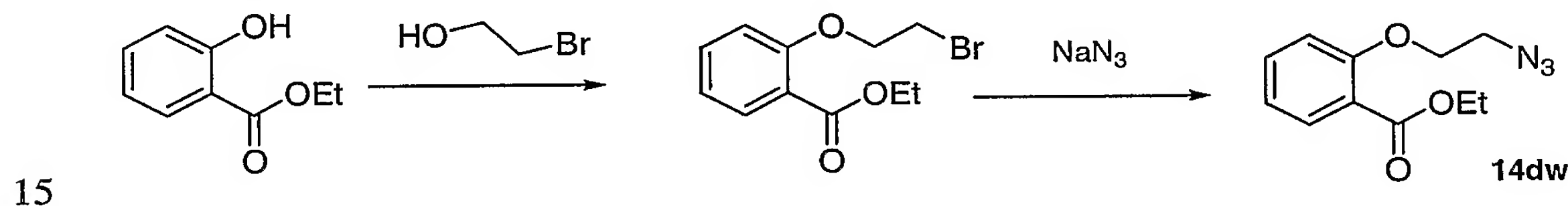
oil. A solution of this crude amine (83 mg) in methanol (3.6 mL) and dichloromethane (3.0 mL) was cooled to 0 °C and treated with triethylamine (0.14 mL, 1 mmol) and triflic azide (1.2 mL of a 0.3 M solution in dichloromethane) and allowed to warm to 23 °C. After 2 h, the reaction mixture was evaporated and purified by preparative thin-layer chromatography (SiO₂, 10% ethyl acetate/dichloromethane) to afford the **63** (60 mg, 0.23 mmol) as a colorless oil.

Synthesis of azide **14ag**

Azide **14ag** was synthesized from 1S, 2S 2-Amino-1-(4-methylsulfanyl-phenyl)-propane-1,3-diol using the procedure described for the synthesis of azide **14bq**.

10 Azides **14a**, **14t**, **14u**, **14at**, **14aw**, **14ax**, **14ay**, **14df**, **14ds**, **14dv**, **14dw**, and **14dz**, were readily synthesized using the Mitsunobu approach shown in Scheme 133 and exemplified below for azide **14dw**.

Scheme 133. Synthesis of azide **14dw**



Synthesis of azide **14dw**

To a mixture of ethyl salicylate (1.0 g, 6.0 mmol), 2-bromoethanol (0.445 mL, 6.06 mmol), and triphenylphosphene (1.8 g, 6.9 mmol) in THF (10 mL) was added diisopropyl azodicarboxylate (DIAD, 1.40 mL, 6.60 mmol) at 0 °C. The mixture was slowly warmed up to RT and stirred for 2 h. The reaction mixture was concentrated and redissolved in ethyl ether (50 mL). It was washed with brine (3 x 50 mL), dried (Na₂SO₄), concentrated and purified by flash chromatography (silica gel, 5% ethyl acetate in hexane) to yield 0.8 g of the intermediate bromoethyl ether. The bromoethyl ether (0.678 g, 2.4 mmol) was dissolved in DMF (5 mL) and sodium azide (0.473 g, 7.2 mmol) was added. The mixture was heated in an oil bath at 70 °C for 2-3 h. The reaction mixture was diluted with ether (50 mL), washed with water (4 x 50 mL), dried (anhydrous Na₂SO₄), and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 10% ethyl acetate in hexane) to yield 0.52 g (89%) of pure azide **14dw**.

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Synthesis of azides 14a, 14t, 14u, 14at, 14aw, 14ax, 14ay, 14df, 14ds, and 14dz

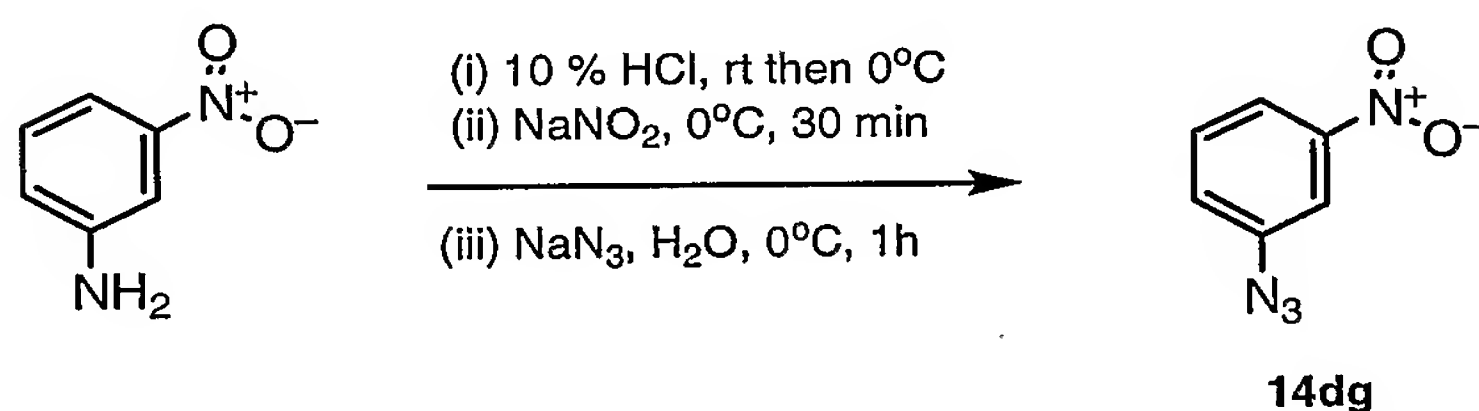
These compounds were prepared from the starting phenols using the same procedure as that described for azide **14dw**.

5 Synthesis of azide 14dv

This azide was prepared from ethyl salicylate using the same procedure as described for azide **14dw** except that 3-bromopropanol was substituted for 2-bromoethanol.

Synthesis of azides 14dg, 14dh, 14di, 14dj, and 14dn.

10 These azides were synthesized from the corresponding anilines by the diazotization as shown in scheme 134 and exemplified below for compound **14dg**.

Scheme 134: Synthesis of Azide **14dg**.

15

Synthesis of azide 14dg.

3-Nitroaniline **4** (2.00 g, 14.20 mmol) was vigorously stirred in 10 % HCl (80 mL) at room temperature until completely dissolved. The solution was cooled to 0°C in an ice-water bath followed by addition of NaNO₂ (1.13 g, 16.33 mmol) stirred for 30 min. A solution of NaN₃ (1.39 g, 21.30 mmol) in H₂O (20 mL) was added drop-wise and stirring continued for another 1h. EtOAc (120 mL) was added to the resulting suspension and the two layers were separated. The organic layer was extracted once with 10 % HCl (100 mL), saturated NaHCO₃ (100 mL), saturated brine (100 mL) and dried over Na₂SO₄. The solvent was evaporated to give **14dg** as a white solid (2.27 g, 97 %).

25

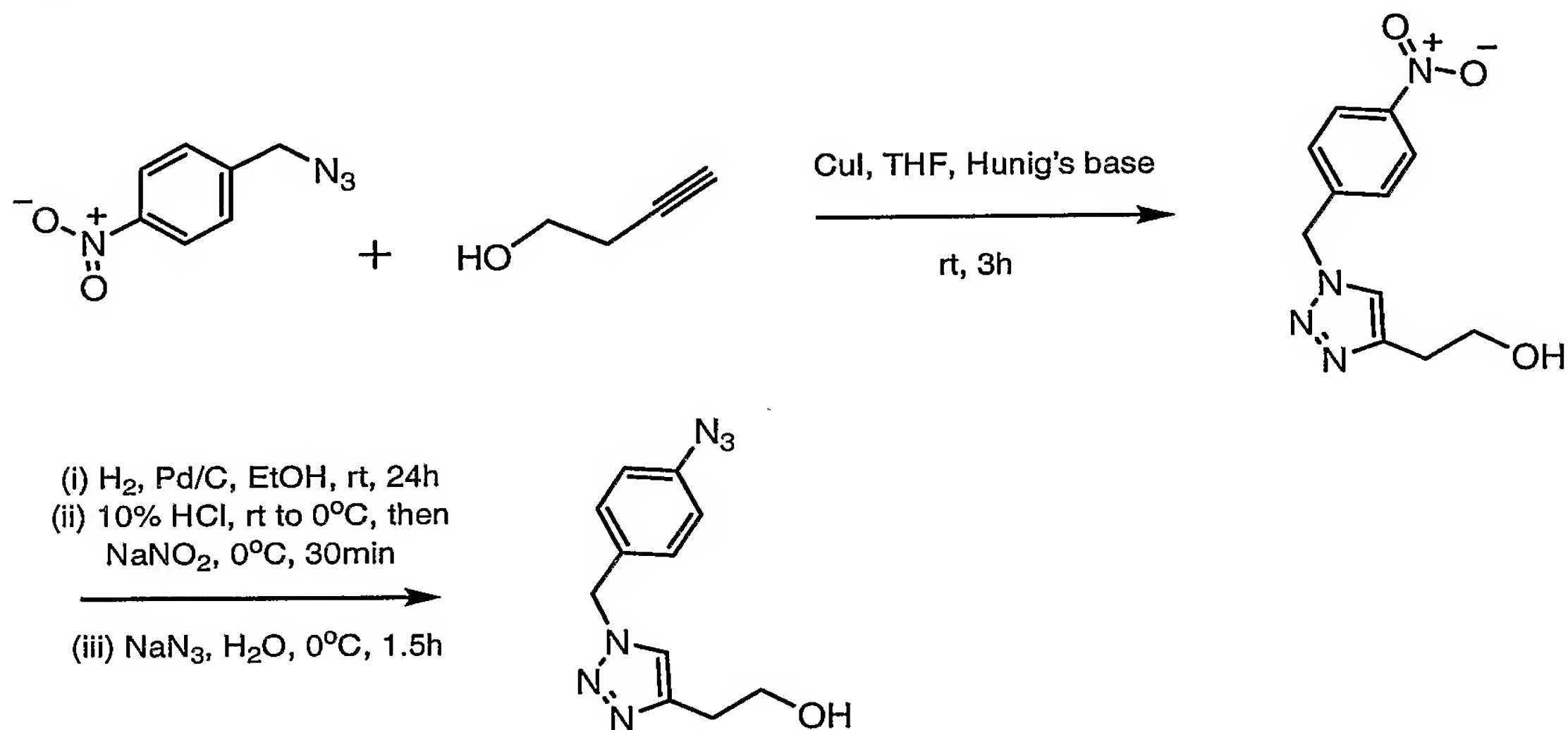
Synthesis of azides 14dh, 14di, 14dj and 14dn.

These azides were synthesized from the corresponding anilines using the conditions described for compound **14dg**.

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Azide **14z** was synthesized from azide **14v** by the sequence shown in Scheme 135.

Scheme 135: Synthesis of Azide **14z**.



5

Synthesis of Azide **14z**:

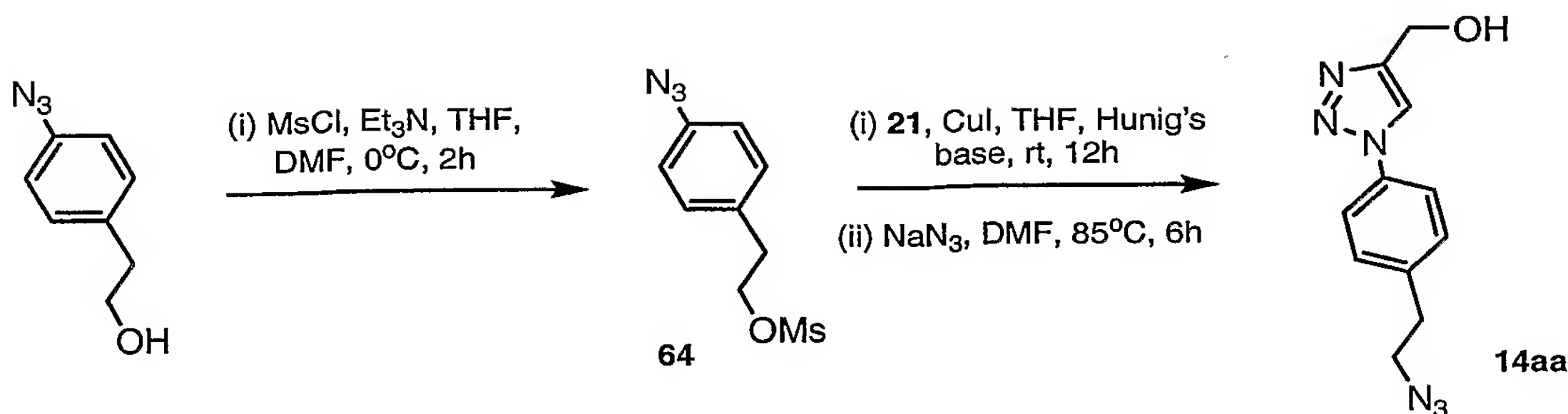
Cycloaddition reaction between azide **14v** (0.66 g, 3.43 mmol) and 1-butyn-4-ol (0.32 mL, 4.12 mmol) in the presence of CuI (0.668 g, 3.43 mmol) in THF (20 mL) and Hunig's base (10 mL) at room temperature within 3h resulted in compound **15**. Crude **15** was reduced with

10 Pd/C (0.10 g, 10 % wt, Degussa) in EtOH (15 mL) under hydrogen atmosphere (balloon) followed by diazotization with NaNO_2 (0.14 g, 2.0 mmol) in 10 % HCl (20 mL) and azidation with NaN_3 (0.17 g, 2.6 mmol) in H_2O (1.0 mL) as described for the synthesis of azide **14dg** gave crude azide **14z**.

15 Azide **14aa** was synthesized according to the methodology illustrated in Scheme 136.

Scheme 136: Synthesis of Azide **14aa**.

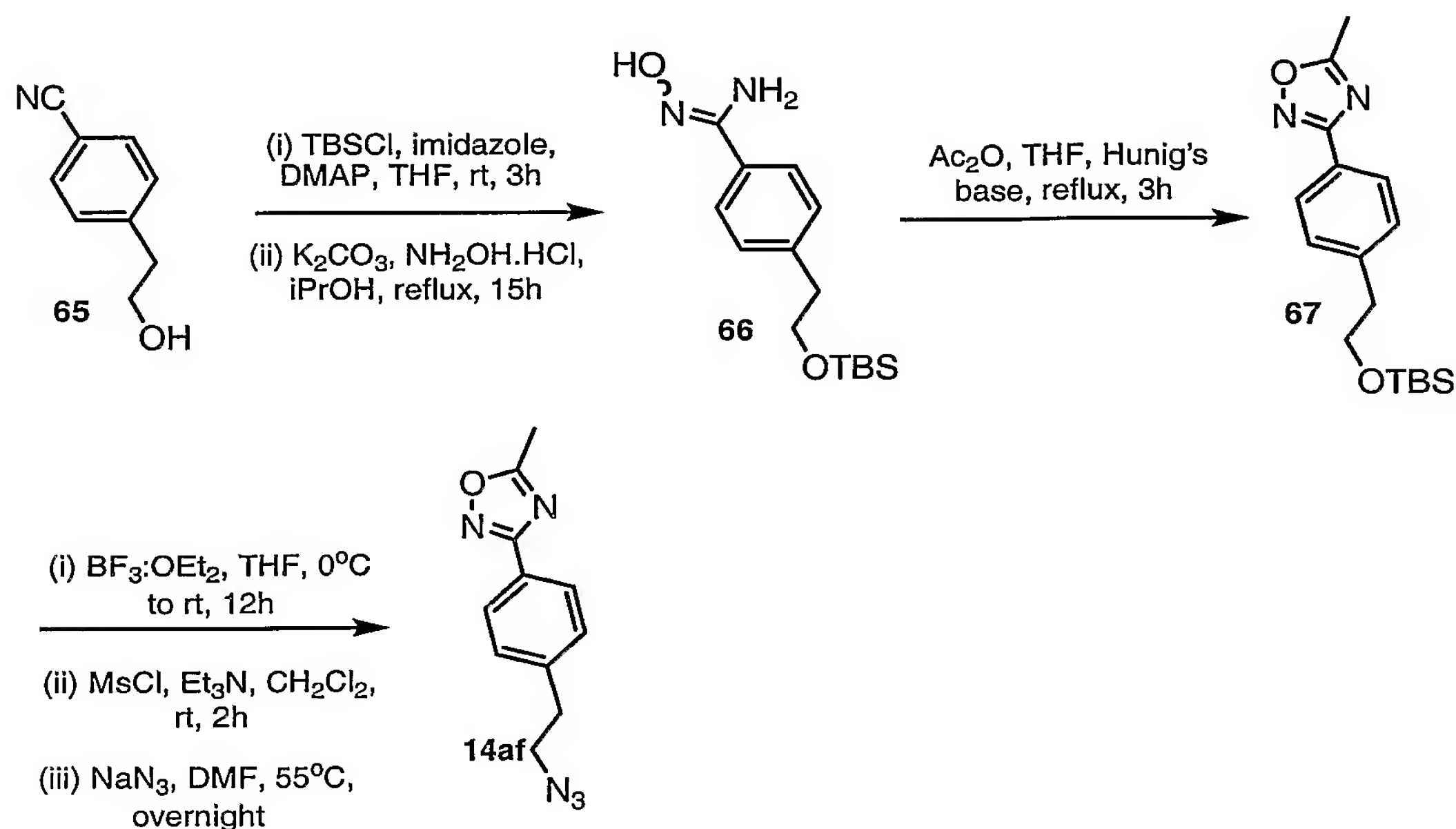
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Synthesis of azide **14aa**:

4-azidophenethyl alcohol (0.6 g, 3.68 mmol) was dissolved in anhydrous THF (15 mL),
 5 DMF (5 mL) and triethylamine (Et₃N) (0.54 mL, 3.7 mmol). The solution was cooled to 0°C in
 ice-water bath, MsCl (0.30 mL, 3.7 mmol) was added and stirring was continued at 0°C for 2h.
 The reaction was quenched with H₂O (1 mL) and concentrated in-vacuo. EtOAc (60 mL) and
 saturated NaHCO₃ (40 mL) were added and the two layers were separated. The aqueous layer
 was washed with EtOAc (2 x 40 mL), the combined organic layer was dried over Na₂SO₄ and
 10 solvent evaporated off to give mesylated derivative as a brown solid. The crude mesylate was
 reacted with propargyl alcohol (0.40 mL, 6.83 mmol) in the presence of CuI (0.54 g, 2.84 mmol)
 in THF (10 mL) and Hunig's base (1 mL) at room temperature for 12h. The reaction was
 worked-up as described for the synthesis of **14v**. To the solution of the crude product in DMF
 (10 mL) was added NaN₃ (0.96 g, 14.7 mmol) and the mixture was heated at 85°C for 6 h. The
 15 reaction was filtered and solvent evaporated off. The residue was partitioned between H₂O (30
 mL) and 5 % MeOH in EtOAc (40 mL). The aqueous layer was extracted with 5 % MeOH in
 EtOAc (5 x 20 mL), the combined organic layer was dried over Na₂SO₄ and the solvent
 evaporated. The crude was purified on silica gel, eluting with CH₂Cl₂/ MeOH 17:1 to furnish
 azide **14aa** as a solid (0.51 g, 57 %).

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Scheme 137: Synthesis of Azide **14af**.**Synthesis of azide 14af:**

5 Cyano-alcohol **65** (0.65 g, 4.42 mmol), imidazole (0.67 g, 9.73 mmol) and DMAP (0.05g, 0.44 mmol) were dissolved in anhydrous THF (20 mL). To this solution was added TBSCl (0.70 g, 4.65 mmol) and stirring continued for 3h during which TLC indicated a quantitative consumption of **65**. CH_2Cl_2 (60 mL) was added and the mixture was extracted with saturated $NaHCO_3$ (1 X 30 mL), saturated brine (1 X 30 mL) and dried over Na_2SO_4 . Solvent

10 was evaporated off to give colorless oil.

To the solution of the crude product in isopropanol (15 mL) was added potassium carbonate (0.28 g, 2.04 mmol) and hydroxylamine hydrochloride (0.29 g, 4.08 mmol) and the resulting mixture was heated at gentle reflux (about $100^\circ C$) for 24h. A substantial formation of a baseline product in addition to a new product ($R_f = 0.31$, $CH_2Cl_2/MeOH$ 30:1) was noticed by

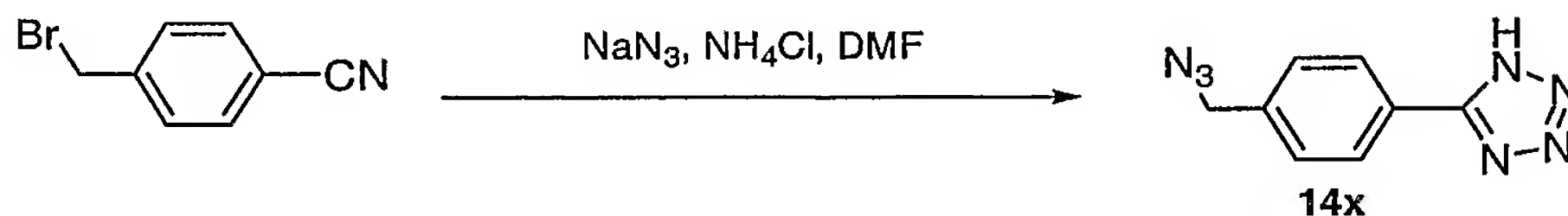
15 TLC. The reaction was filtered and solvent was evaporated off to give white solid. MS (ESI) analysis confirmed the presence of the desired carboxami-doxime **66** ($M + H^+ = 295.1$) and the corresponding TBS-protected product ($M + H^+ = 181.0$) in about 1:1 ratio.

Half of the crude **66** (about 2.2 mmol based on **65**) was dissolved in THF (10 mL) and Hunig's base (5 mL). To this solution was added acetic anhydride (1.05 mL, 11.0 mmol) and the

20 mixture was heated under reflux for 3h. Solvent was evaporated off and the residue was

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partitioned between CH_2Cl_2 (40 mL) and saturated NaHCO_3 (30 mL). The two layers were separated, the organic layer was extracted with saturated NaHCO_3 (2 x 30 mL), saturated brine (1 x 30 mL) and dried over Na_2SO_4 . Solvent was evaporated off and the crude was purified on silica gel, eluting with EtOAc/Hexanes 1: 8 to 1:6 to 1:4 to 1:3 to give oxidiazole **67** (0.040 g, 6 %). To a solution of oxidiazole **67** (0.039 g, 0.12 mmol) in THF (3 mL) was added $\text{BF}_3\cdot\text{OEt}_2$ (0.16 mL, 1.26 mmol) with stirring at 0°C . The reaction was allowed to warm up to room temperature and stirring continued overnight. Ethanol was added to destroy excess $\text{BF}_3\cdot\text{OEt}_2$ and solvent was evaporated off. The residue was taken up into CH_2Cl_2 (40 mL), extracted with saturated NaHCO_3 (2 X 25 mL) and dried over Na_2SO_4 . Solvent was evaporated off and the crude was used without further purification. The crude was dissolved in CH_2Cl_2 (2 mL) and Et_3N (0.05 mL, 0.36 mmol). To this solution was added MsCl (0.04 mL, 0.48 mmol) at room temperature with stirring. Stirring continued at room temperature for 2h, and the reaction was partitioned between CH_2Cl_2 (40 mL) and saturated NaHCO_3 (30 mL). The two layers were separated, the organic layer was extracted with saturated NaHCO_3 (2 X 30 mL), saturated brine (1 X 20 mL), dried over Na_2SO_4 , and solvent was evaporated off. The crude was dissolved in DMF (3 mL), NaN_3 (0.10 g, 1.5 mmol) was added and the mixture was heated at 55°C overnight. Diethyl ether (50 mL) was added, the solution was extracted with saturated NaHCO_3 (3 X 30 mL), saturated brine (1 X 30 mL), dried over Na_2SO_4 , and solvent was evaporated off. The crude was purified on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 120:1 to give azide **14af** as colorless thick oil (0.018 g, 66 %).

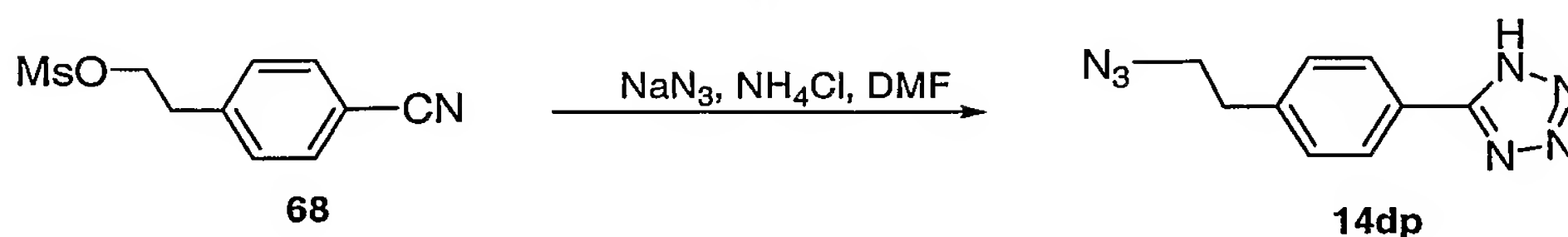
Scheme 138 Synthesis of Azide **14x**Synthesis of azide **14x**

A mixture of α -bromo-p-tolunitrile (196 mg, 1 mmol), NH_4Cl (107 mg, 2 mmol) and NaN_3 (260 mg, 4 mmol) in DMF (2 mL) was heated at 120°C for 8 h. The reaction was then diluted with CH_2Cl_2 . The inorganic salt was removed by filtration, the resulted solution was

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concentrated and purified by flash column (10:1:0.1/CH₂Cl₂:MeOH:NH₃·H₂O) to provide azide **20** (180 g, 90 % yield).

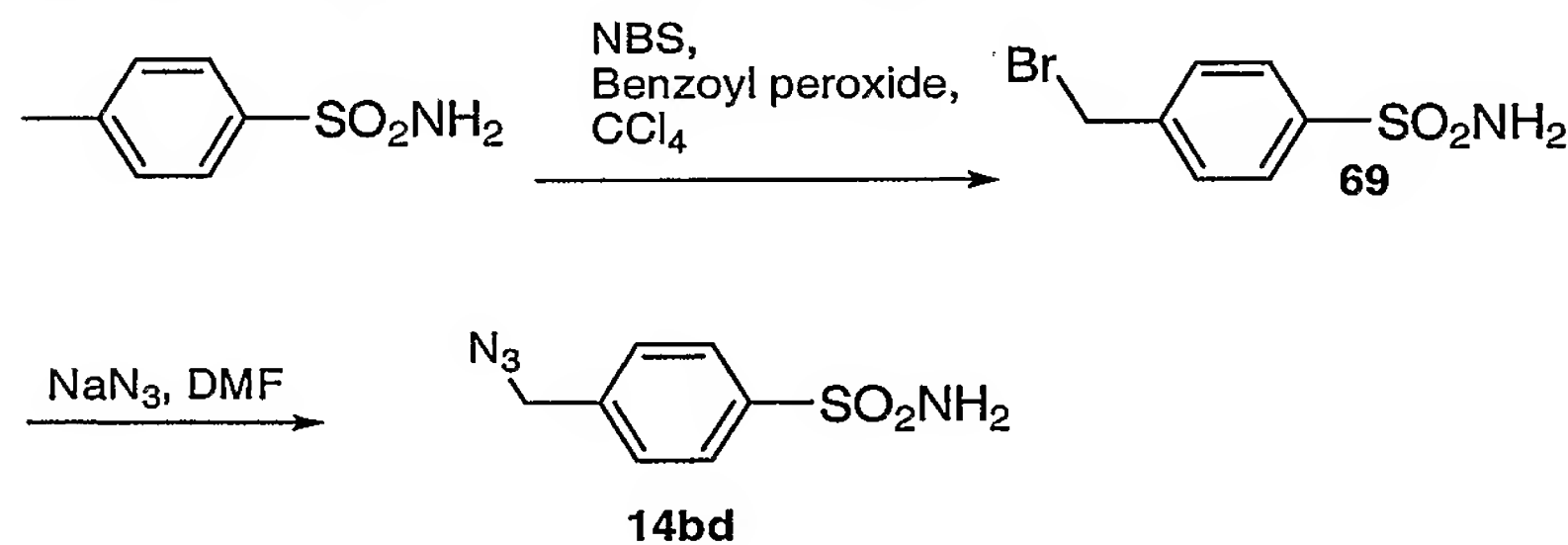
Scheme 139 Synthesis of Azide 14dp



Synthesis of azide 14dp

A mixture of mesylate **68** (700 mg, 3.1 mmol), NH₄Cl (332 mg, 6.2 mmol) and NaN₃ (808 mg, 12.4 mmol) in DMF (5 mL) was heated at 120 °C for 4 h. The reaction was then diluted
 10 with CH₂Cl₂. The inorganic salt was removed by filtration, the resulting solution was concentrated and the product purified by flash column chromatography (10:1:0.1/CH₂Cl₂:MeOH:NH₃·H₂O) to provide azide **14dp** (600 mg, 90 % yield).

Scheme 140 Synthesis of Azide 14bd

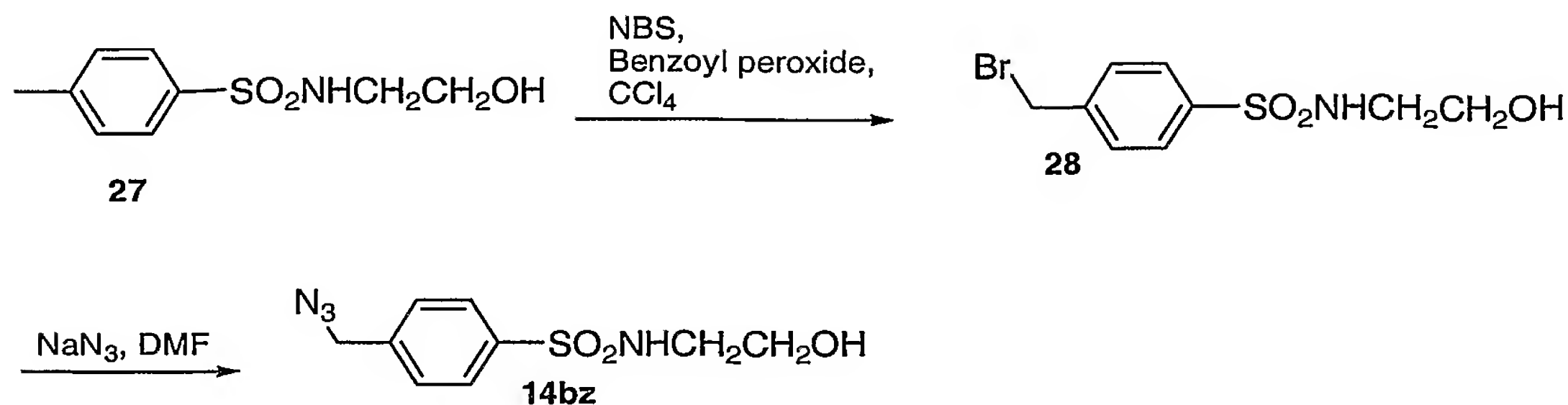


Synthesis of azide 14bd

A mixture of *p*-toluenesulfonamide (6.84 g, 40 mmol), N-bromosuccinimide (7.12 g, 40 mmol) and benzoyl peroxide (0.29 g, 1.2 mmol) in carbontetrachloride (CCl₄) (100 mL) was
 20 refluxed for 3h. The reaction mixture was concentrated and the residue was extracted with EtOAc. The resulting crude product was crystallized in CH₂Cl₂ to provide **69** (2.60 g, 26 % yield). A mixture of **69** (150 mg, 0.6 mmol) and NaN₃ (156 mg, 2.4 mmol) in DMF (2 mL) was heated at 80 °C for 6 h. The reaction was then diluted with ethyl acetate, washed with brine, dried (MgSO₄) and evaporated to provide azide **14bd** (110 mg, 86 %

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Scheme 141 Synthesis of Azide **14bz****Synthesis of azide 14bz**

- 5 Azide **14bz** was prepared from the reaction of bromide **28** and sodium azide following the procedure for the synthesis of **14bd**. Yield, 90 %. Bromide **28** was prepared from the reaction of *N*-(2-hydroxyethyl)-*p*-toluenesulfonamide and *N*-bromosuccinimide following the procedure for the synthesis of **17**. Yield, 23 %.

10 **Synthesis of azide 14bm**

Azide **14bm** was prepared from 2-fluoro-4-sulfonamido toluene according to the procedure described above for azide **14bd**.

Synthesis of azide 14bh

- 15 Azide **14bh** was prepared from 3-fluoro-4-sulfonamido toluene according to the procedure described above for azide **14bd**.

Synthesis of azide 14bo

- 20 Azide **14bo** was prepared from 1-*p*-tolyl-ethanone according to the procedure described above for azide **14bd**.

Synthesis of azide 14cm

Azide **14cm** was prepared from 4-dimethylaminosulfonyl toluene according to the procedure described above for azide **14bd**.

25

Synthesis of azide 14cn

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Azide **14cn** was prepared from 4-methylaminosulfonyl toluene according to the procedure described above for azide **14bd**.

Synthesis of azide **14cr**

5 Azide **14cr** was synthesized from 3-(2-Fluoro-4-methyl-phenyl)-5-hydroxymethyl-oxazolidin-2-one as described above for azide **14bd**.

Synthesis of azide **14cp**

10 Azide **14cp** was synthesized from N-[3-(2-Fluoro-4-methyl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide as described above for azide **14bd**.

Synthesis of azide **14bl**

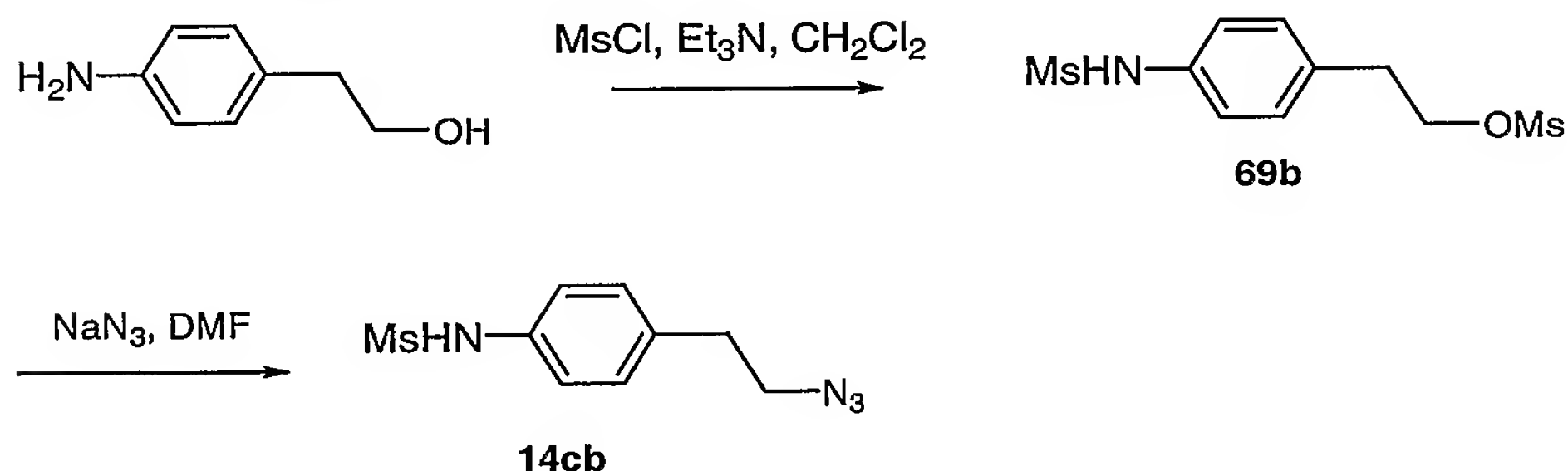
Azide **14bl** was prepared from 3-methoxy-4-sulfonamido toluene according to the procedure described above for azide **14bd**.

15

Synthesis of azide **14ca**

Azide **14ca** was prepared from the reaction of *p*-toluamide and *N*-bromosuccinimide followed by reaction with sodium azide following the procedure for the synthesis of **14bz**. Yield, 40 %.

20 Scheme 142 Synthesis of azide **14cb**



Synthesis of azide **14cb**

25 Methanesulfonyl chloride (1.7 mL, 22 mmol) was added to a solution of 4-aminophenylethyl alcohol (1.37 g, 10 mmol) and Et₃N (2.5 g, 25 mmol) in CH₂Cl₂ (20 mL) at 0 °C. The mixture was kept stirring at 0 °C for 2 h. The reaction mixture was washed with brine, dried over MgSO₄ and concentrated to provide **69b** (2.6 g, 89 % yield).

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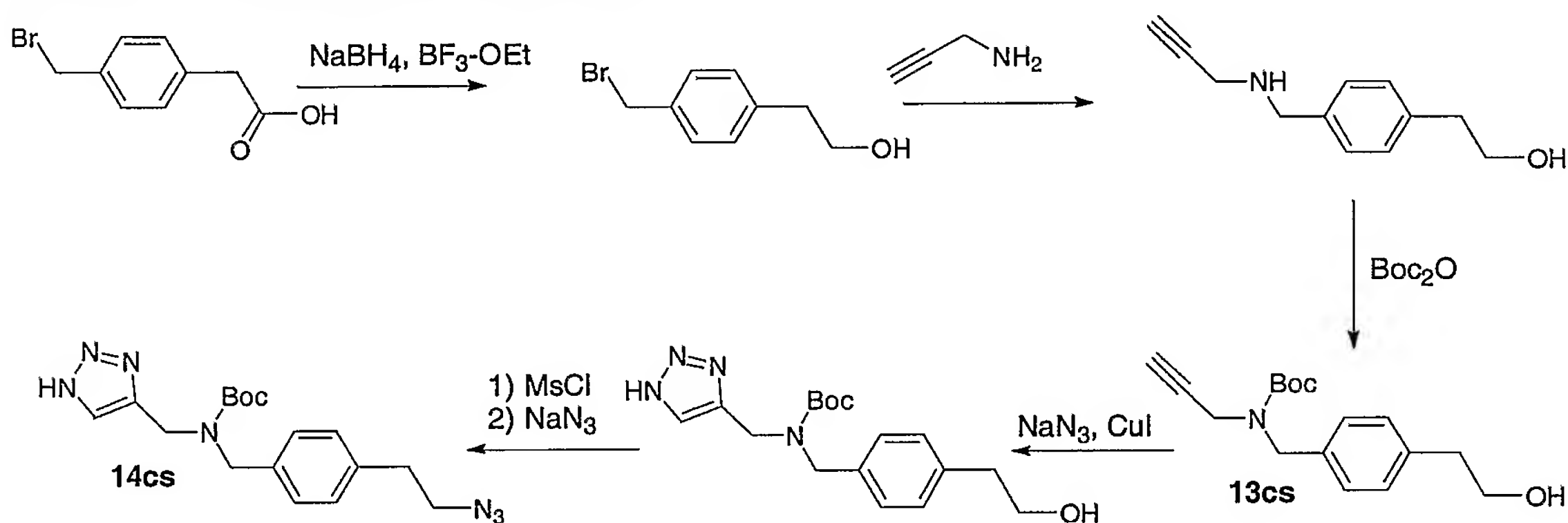
Azide **14cb** was prepared from the reaction of bis-mesylate **69b** and sodium azide following the procedure for the synthesis of **14bd**. Yield, 90 %.

Synthesis of azide **14cq**

5 Azide **14cq** was synthesized from acetic acid 3-[2-fluoro-4-(2-hydroxy-ethyl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl ester according to the procedure described for azide **14cb**.

Azide **14cs** was synthesized from 4-bromomethylphenyl acetic acid by the route shown in Scheme 143.

10 Scheme 143 Synthesis of Azide **14cs**



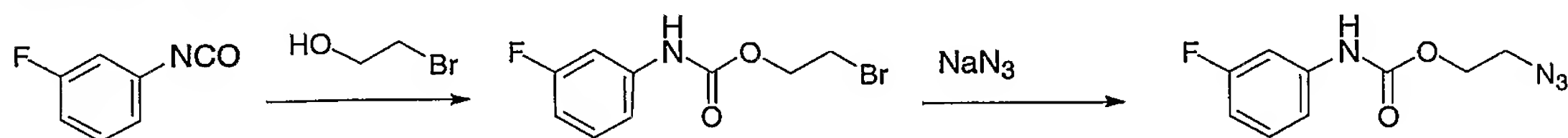
Synthesis of azide **14cs**

4-Bromomethylphenyl acetic acid (1.15 g, 5 mmol) was treated with NaBH₄, BF₃·OEt according to the conditions described below in the synthesis of azide **14b**. The crude *p*-bromomethyl phenethyl alcohol was treated with propargyl amine hydrochloride (0.85g, 9.3 mmol) in Hunig's base at rt for 2h. The reaction mixture was concentrated and the crude residue dissolved in a 2:1 THF water mixture (30 mL) and treated with t-butoxycarbonyl (Boc) anhydride (1.1g) and K₂CO₃ (0.83g) for 12h. The reaction mixture was partitioned between water and EtOAc, the organic layer was dried, filtered and concentrated to give a residue which was purified by preparative TLC (elution with 15:1:0.1 CH₂Cl₂:MeOH:NH₄OH to give 0.89g of the intermediate **13cs**. Alkyne **13cs** (0.62g, 2.15 mmol) was converted to the corresponding triazole by reaction with sodium azide and NHCl as described above in the synthesis of **14dp**. The triazole product was treated with mesyl chloride and azide as described below for the synthesis of azide **14dx** to afford the azide **14cs** as a colorless oil.

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. Azides **14o-14r** were synthesized from the corresponding phenylisocyanates by reaction with 2-bromoethanol followed by displacement with azide ion. The procedure given below for azide **14o** is typical.

5 Scheme 144



Synthesis of azide **14o**

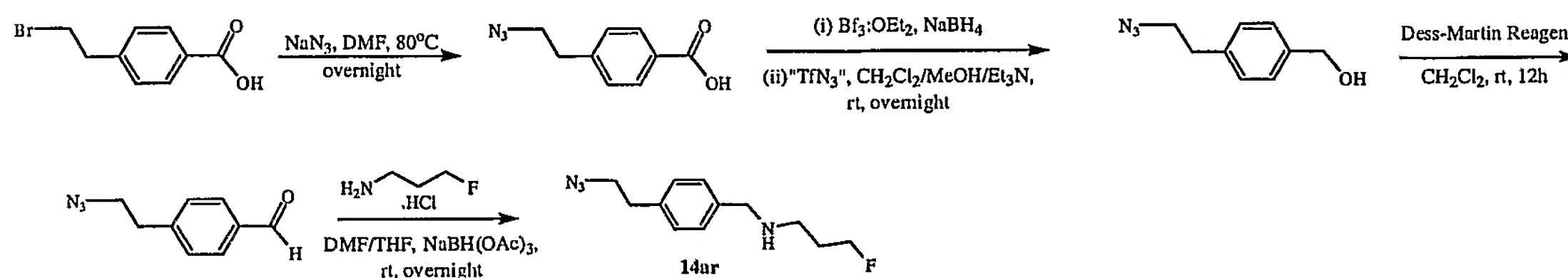
To a stirred solution of 3-fluorophenylisocyanate (2g, 14.6 mmol) in toluene was added
 10 bromoethanol (2 mL, 29.2 mmol). The reaction mixture was refluxed for 7h. The reaction
 mixture was diluted with ether (100 mL) and washed with water (3 x 100 mL). The organic
 extract was dried, filtered and concentrated and the residue dissolved in DMF (30 mL). NaN_3
 (2.5g, 30.5 mmol) was added and the reaction mixture was stirred at 70°C for 4h. The reaction
 mixture was partitioned between ether and water. The organic layer was separated and washed
 15 with water (3 x 100 mL) then dried and concentrated. The crude product was purified by silica
 gel chromatography (elution with 9:1 Hexane EtOAc) to give **14o** as a white solid (2.4g).

Azides **14p**, **14q**, and **14r** were synthesized from the corresponding isocyanates under the same
 condition described for azide **14o**.

20

Azide **14ar** was synthesized from 4-(2-bromoethyl)benzoic acid by the sequence illustrated in
 Scheme 145 below.

Scheme 145 Synthesis of azide **14ar**



25

Synthesis of azide **14ar**

A mixture of 4-(2-Bromoethyl)benzoic acid (1.0 g, 4.40 mmol) and sodium azide (0.72 g, 11.0 mmol) in DMF (10 mL) was heated at 80°C for about 12h. The solvent was evaporated and

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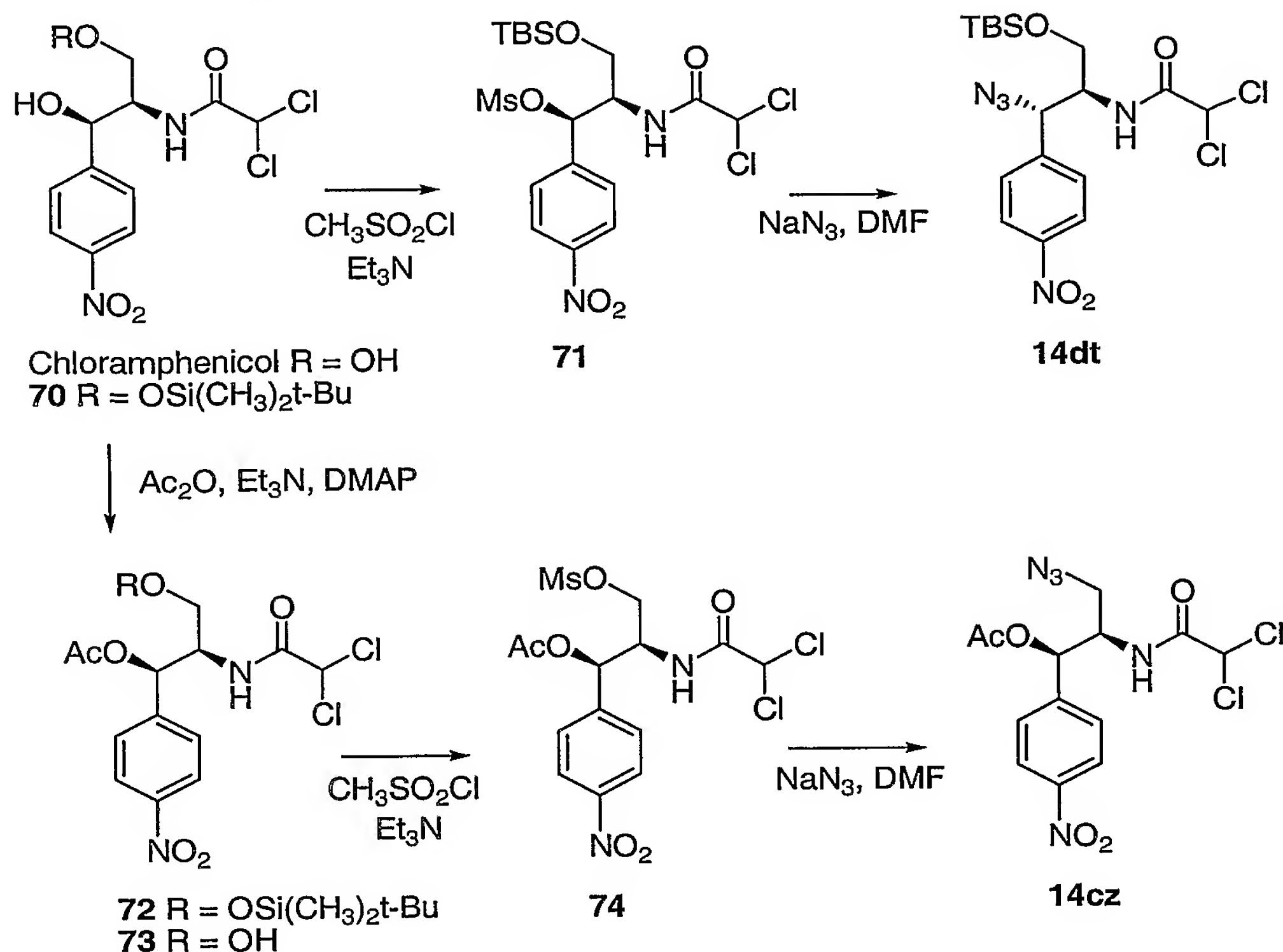
the residue was suspended in cold water (40 mL) acidified with few drops of glacial acetic acid. The suspension was filtered, the residue was washed with cold water (40 mL) acidified with few drops of glacial acetic acid and dried in vacuo at 40°C to give carboxylic acid as white solid (0.8 g, 95 %) (Rf = 0.51, EtOAc/Hexanes/MeOH 4:1:0.02).

5 To a solution of this carboxylic acid (0.70 g, 3.87 mmol) in anhydrous THF (8 mL) was added 1M BH₃:THF (12 mL, 12.0 mmol) at 0°C. Stirring was continued at 0°C for 1h and the reaction was warmed up to room temperature. The mixture was stirred at room temperature for 14h. TLC (visualization with ninhydrin stain) showed azide reduction took place. NaBH₄ (0.46 g, 12 mmol) and BF₃:OEt₂ (1.6 mL, 12 mmol) were added and stirring continued for about 18h
10 to ensure a complete azide reduction. Excess boron trifluoride etherate was destroyed with ethanol, and the mixture filtered. The filtrate was evaporated to afford a semi solid. The crude was treated with freshly prepared triflic azide (12 mmol) as described for the synthesis of azide **14s**. The crude was purified on silica gel eluting with EtOAc/Hexanes 2:3 to afford 4-(2-azidoethyl)-benzyl alcohol as clear oil (0.56 g, 82 %) (Rf = 0.53, EtOAc/Hexanes 2:3).

15 A mixture of azido-alcohol this (0.40 g, 2.26 mmol) and Dess-Martin reagent (1.25 g, 2.93 mmol) in CH₂Cl₂ (15 mL) was stirred at room temperature overnight. The reaction was quenched with 10 % Na₂S₂O₃: saturated NaHCO₃ (1:1) (30 mL), CH₂Cl₂ (30 mL) was added and the two layers separated. The organic layer was washed with 10 % Na₂S₂O₃: NaHCO₃ (1:1) (2 X 30 mL), saturated NaHCO₃ (2 X 30 mL) and dried over Na₂SO₄. Solvent was evaporated off and
20 the residue was purified on silica gel, eluting with EtOAc/Hexanes 1:6 to give 4-(2-azidoethyl)-benzaldehyde as clear oil (0.23 g, 58 %) (Rf = 0.46, EtOAc/Hexanes 1:4).

A mixture of this azido-aldehyde (0.23 g, 1.31 mmol) and 3-fluoropropyl amine hydrochloride (0.25 g, 2.20 mmol) in DMF (4 mL) and THF (10 mL) was stirred at room temperature for 30 min. NaBH(OAc)₃ (0.51 g, 2.40 mmol) was added and stirring was continued
25 at room temperature for about 18h. MeOH (20 mL) was added, the suspension was filtered and the filtrate evaporated off to give oily residue. The residue was partitioned between 10 % MeOH in CH₂Cl₂ (40 mL) and water (25 mL), the two layers were separated and the organic layer was dried over Na₂SO₄. Solvent was evaporated off and the residue was purified by preparative TLC (2000 micron plate) eluting with CH₂Cl₂/MeOH (2 N NH₃) 18:1 to give azide **14ar** as light
30 yellow oil (0.077 g, 25 %) (Rf = 0.34, CH₂Cl₂/MeOH (2 N NH₃) 18:1). MS (ESI) M/E; M+H⁺ 237.0.

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Scheme 146 Synthesis of azides **14dt** and **14cz****Synthesis of alcohol **70****

- 5 To a mixture of chloramphenicol (6.26 g, 20 mmol) and tert-butyldimethylsilyl chloride (3.32 g, 22 mmol) in CH₂Cl₂ (40 mL) was added imidazole (1.70 g, 25 mmol). After stirring at room temperature for 4 h, the solution was quenched with saturated NaHCO₃ solution. The organic phase was washed with brine, dried over anhydrous MgSO₄ and concentrated under reduced pressure. After purification by flash chromatography (silica gel, hexane: ethyl acetate/6:1), 8.85 g of white crystalline **70** was obtained in a yield of 96%.
- 10

Synthesis of mesylate **71**

- 15 Methanesulfonyl chloride (0.32 g, 2.75 mmol) was added drop wise to a solution of **70** (1.09 g, 2.5 mmol) and Et₃N (0.51 g, 5.0 mmol) in CH₂Cl₂ (5 mL) at 0 °C. The mixture was kept stirring at 0°C for 2 h and at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc. The EtOAc solution was washed with brine,

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dried over anhydrous MgSO_4 and concentrated under reduced pressure to afford 1.22 g of **71** as light yellow oil. Yield: 95%.

Synthesis of azide **14dt**

5 A mixture of mesylate **71** (1.32g, 2.5 mmol) and sodium azide (0.65g, 10 mmol) in DMF (5 ml) was stirred at 50-60°C for 5 h. The reaction was quenched with water. The solution was extracted with EtOAc, washed with brine, dried over anhydrous MgSO_4 and concentrated in vacuum. The crude product was purified by chromatography (silica gel, hexane: ethyl acetate/15:1) to afford 0.75 g of light yellow oil **53**. Yield: 65%. MS (ESI) m/e 460 (M-H)⁺.

10

Synthesis of acetate **72**

 Triethylamine (2.5 mL, 17.9 mmol) was added to a solution of **70** (3.3 g, 7.6 mmol), acetic anhydride (2.4 g, 23.3 mmol) and 4-dimethylaminopyridine (60 mg, 0.49 mmol) in CH_2Cl_2 (30 mL) at 0°C. After stirring at same temperature for 2 h, the reaction was diluted with
15 CH_2Cl_2 , washed with saturated NaHCO_3 , dried over anhydrous MgSO_4 and concentrated. Flash chromatography (silica gel, hexane: ethyl acetate/6:1) of crude product afforded 3.4 g of white crystalline **72**. Yield: 94%.

Synthesis of alcohol **73**

20 To a solution of **72** (3.59 g, 7.5 mmol) in THF (50 mL) was added a solution of 1.0 M TBAF in THF (7.5 mL, 7.5 mmol). The reaction mixture was stirred at room temperature under argon atmosphere for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved with EtOAc and washed with brine. The organic phase was dried (MgSO_4), concentrated and purified by chromatography (silica gel, hexane: ethyl acetate/4:1) to afford 2.40
25 g of light yellow oil **73**. Yield: 88%.

Synthesis of mesylate **74**

 Triethylamine (1.8 mL, 12.7 mmol) was added to a solution of **73** (2.32 g, 6.36 mmol) and methanesulfonyl chloride (0.80 g, 7.0 mmol) in CH_2Cl_2 (20 mL) at 0°C. After stirring at 0°C
30 for 2 h, the solvent was removed under reduced pressure, the residue was dissolved in EtOAc and washed with brine. The organic phase was dried (MgSO_4) and concentrated under reduced pressure to afford 2.8 g of **74** as light yellow oil. Yield: 99%.

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Synthesis of azide 14cz

The mixture of mesylate **74** (3.0 g, 6.8 mmol) and sodium azide (1.76 g, 27.1 mmol) in DMF (15 ml) was stirred at 60°C under argon atmosphere for 2 h. The reaction was quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried (MgSO₄), concentrated and purified by chromatography (silica gel, hexane : ethyl acetate/4:1) to afford 1.65 g light yellow solid **57**. Yield: 63%. MS (ESI) *m/e* 388 (M-H)⁺.

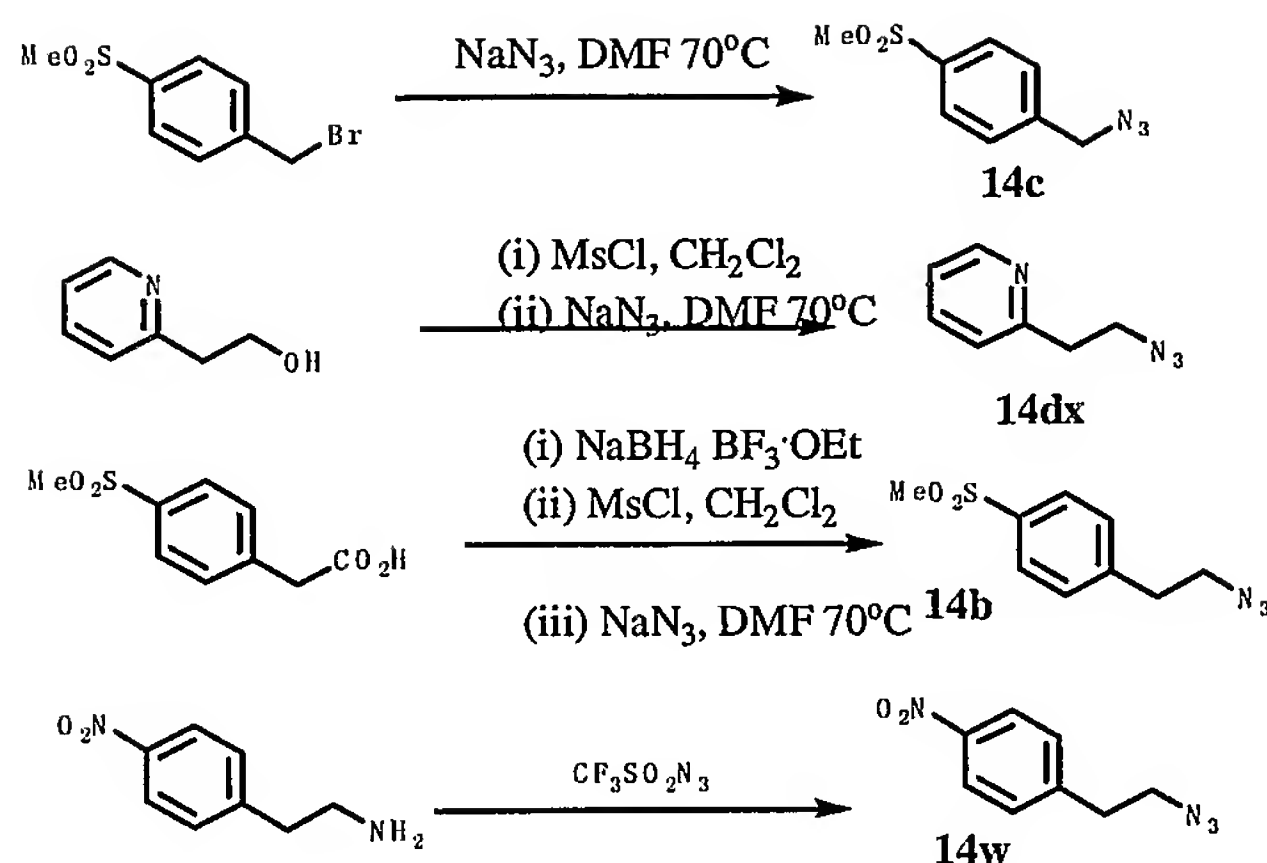
Synthesis of azide 14cx

The synthesis of this azide is described in the patent application WO2004029066A3.

The majority of the azides in Table 11 including all those for which synthetic details are not provided in the preceding paragraphs were synthesized according to known procedures using the reactions shown in the schemes above. The specific route used for each azide was determined by the available commercial starting materials. When possible azides were produced from the corresponding substituted alkyl bromides by direct displacement with azide ion, this method is exemplified in the synthesis of azide **14c** described below. When the required alkyl bromides were not readily available, the compounds were derived from substituted alkanols: to accomplish this the alcohols were first activated as their sulfonyl ester derivatives and then substituted with azide ion. This procedure is exemplified below for the synthesis of azide **14dx**. If neither the required bromides or alkanols were commercially available, the azides were synthesized from the corresponding carboxylic acids by reduction with borohydride to the corresponding alcohols. The resulting alkanols were then treated as above to yield the azides. The chemistry employed to convert a carboxylic acid to an azide is exemplified below for compound **14b**. Finally, some azides of Table 11 were synthesized from the corresponding substituted alkyl amines by reaction with triflic azide. An example of this procedure is provided for the synthesis of azide **14w** below.

Scheme 147. Synthesis of azides **14c**, **14dx**, **14d** and **14w**.

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Synthesis of azide 14c

To a solution of 4-methylsulfonyl benzyl bromide (1 g, 4.0 mmol) in DMF (20 mL) was added NaN_3 (0.52g, 8.0 mmol). The mixture was stirred at rt for 1h, then poured into 200 mL of a 1:1 water-ether mixture. The aqueous layer was separated and extracted with ether (2 x 50 mL) and the combined organic extracts dried (Na_2SO_4), and concentrated under reduced pressure to yield a crude product. Purification by silica gel chromatography (elution with 30% EtOAc in hexanes) afforded the pure azide as a white solid (0.52g, 2.5 mmol)

Synthesis of azides 14dx

To a solution of 2-(2-hydroxyethyl)pyridine (2 g, 16.2 mmol) and diisopropylethylamine (5.6 mL, 32.4 mmol) in CH_2Cl_2 (40 mL) was added methanesulfonyl chloride (1.4 mL, 17.8 mmol) at 0°C . The mixture was warmed to rt, stirred for 3h, then quenched with water and diluted with CH_2Cl_2 (30 mL). The organic layer was washed with NaHCO_3 (2 x 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield 3.2 g of the crude mesylate which was of suitable purity to be used in subsequent reactions without purification. The above mesylate was converted to azide 14dx using the same procedure used to synthesize azide 14dw from the bromoethyl ether of ethyl salicylate.

Synthesis of azide 14d

To a solution of 4-methylsulfonyl phenyl acetic acid (1 g, 4.7 mmol) in THF (25 mL) was added NaBH_4 (0.54g, 14.1 mmol) after 5 minutes $\text{BF}_3\cdot\text{OEt}$ (2.4 mL, 18.8 mmol) was added and the reaction mixture allowed to stir 16h at rt. The reaction was quenched with MeOH,

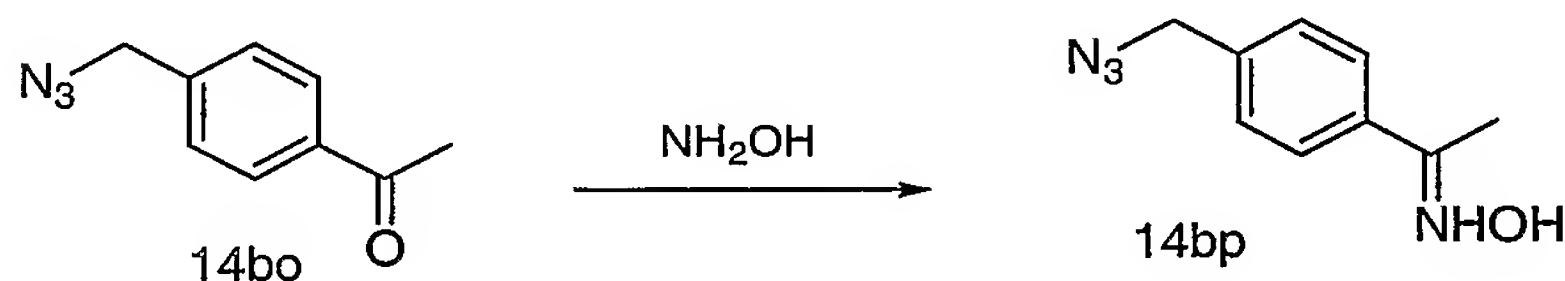
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filtered and concentrated *in vacuo*, then suspended in CH₂Cl₂. The solid was filtered, dried, and re-suspended in CH₂Cl₂ (10 mL). Triethylamine (1.3 mL, 9.4 mmol) was added followed by MsCl (0.6 mL, 7.0 mmol). After 4h additional triethylamine (1.3 mL, 9.4 mmol) and MsCl (0.6 mL, 7.0 mmol) were added and stirring was continued for 16h. The reaction mixture was diluted with 50 mL CH₂Cl₂, washed with saturated NaHCO₃ and with brine, then dried (Na₂SO₄), filtered and concentrated.

The crude mesylate was dissolved in DMF (10mL), 0.61g NaN₃ was added and the reaction stirred at 80°C for 2h. The reaction mixture was partitioned between ether and water and the aqueous layer further extracted with ether (3 x 30 mL). The combined organic extracts were washed with brine (100 mL), dried (Na₂SO₄), filtered, and concentrated to give a crude product which was purified by silica gel chromatography (elution with 40% EtOAc in hexanes) to afford **14d** as a white solid (0.70g, 12 mmol).

In a few cases the azides of Table 11 were synthesized by modification of other azides that had been synthesized according to the methodologies above:

Scheme 148



Synthesis of azide **14bp** from azide **14bo**.

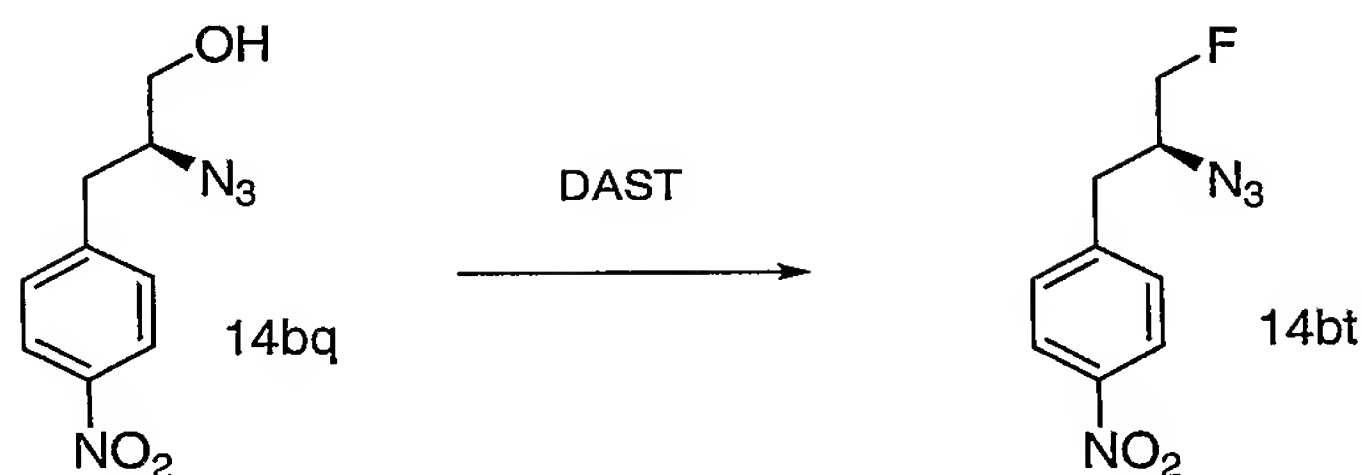
To a solution of azide **14bo** (0.18 g, 1 mmol) in MeOH (5 mL) was added HONH₂·HCl (0.35g, 5 mmol) and triethylamine (0.35 mL, 2.5 mmol). The mixture was refluxed for 8h, then diluted with EtOAc, washed with water and brine. The organic extracts were dried (Na₂SO₄), filtered and concentrated to afford **14bp** as a white solid (180mg).

Synthesis of azide **14bn** from azide **14bk**

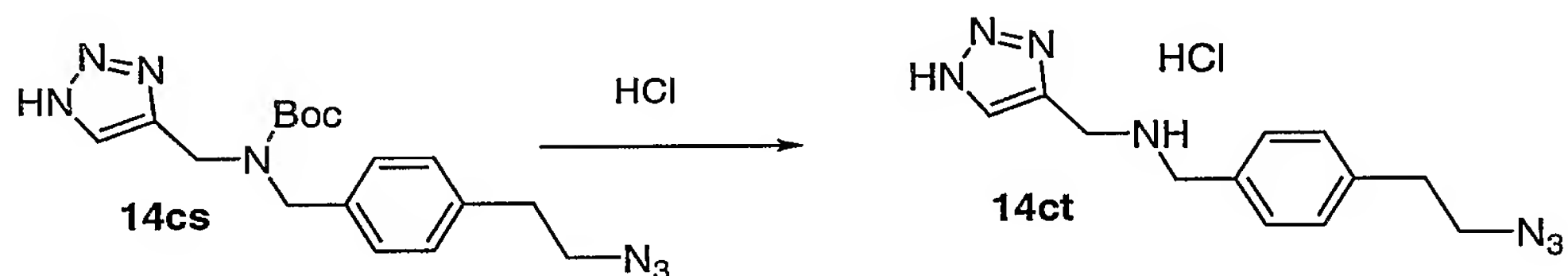
Azide **14bn** was prepared from **14bk** according to the procedure described for the synthesis of azide **14bp**

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Scheme 149

**Synthesis of azide 14bt from azide 14bq**

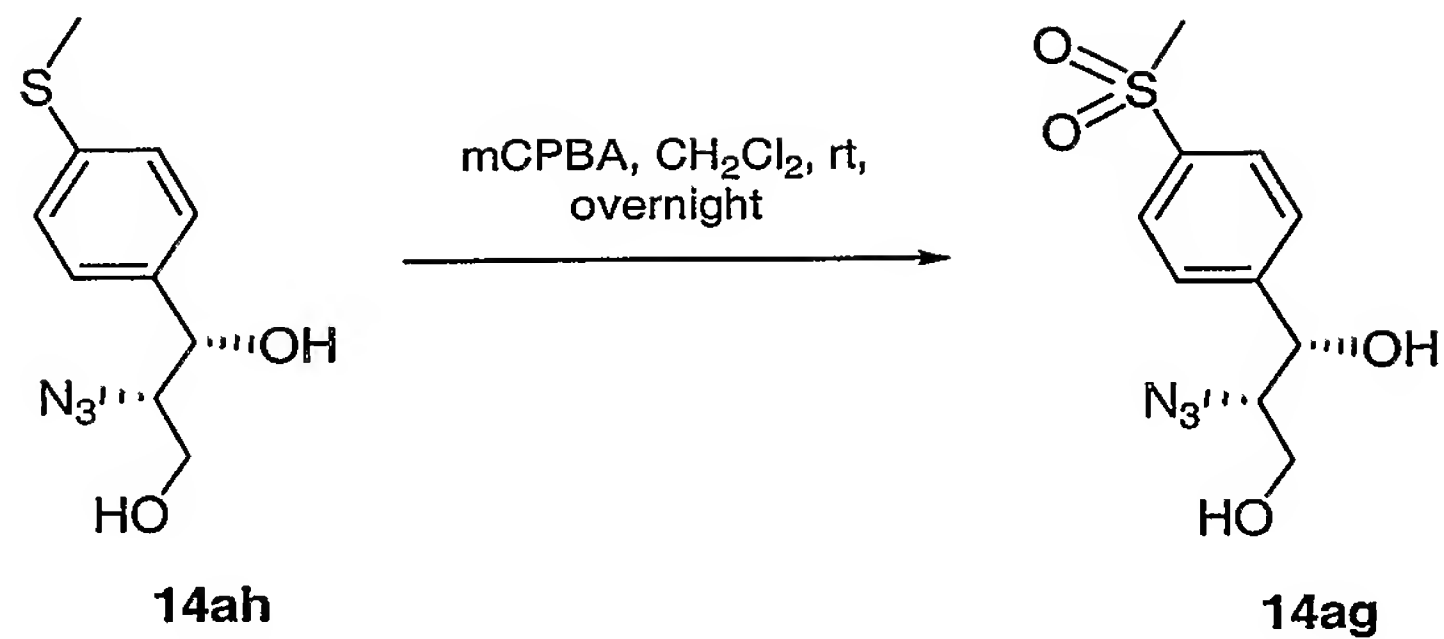
- 5 To a stirred -78°C solution of azide **14bt** (111 mg, 0.5 mmol) in CH_2Cl_2 was added (diethylamino)sulfur trifluoride (DAST) (0.1 mL, 0.82 mmol). The reaction was stirred at -78°C for 2h, then allowed to warm to rt and stirred for 14h. The reaction mixture was poured into water and extracted with CH_2Cl_2 . The organic extracts were dried, filtered, and concentrated to give **14bq** as a solid (36mg, 0.16 mmol).

10 **Scheme 150****Synthesis of azide 14ct from azide 14cs**

- 15 To a stirred solution of **14ct** (0.21g) in CH_2Cl_2 (10mL) was added 4M HCl in 1,4-dioxane (2 mL) the mixture was stirred at rt for 10h, then concentrated under reduced pressure to afford the HCL salt of azide **14cz** as a white solid (0.15g).

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Scheme 151



5 Synthesis of azide **14ah** from **14ag**

To a solution of azide **14ah** (0.27 g, 1.1 mmol) in CH₂Cl₂ (15 mL) was added mCPBA (1.10 g, 4.5 mmol) and the mixture was stirred at room temperature overnight. Solvent was evaporated and the crude was purified on silica gel eluting with CH₂Cl₂/MeOH 20:1 to 15:1 to 12:1 to give azide **14ag** as colorless paste that solidified on standing (0.26 g, 87 %).

Example 11 synthesis of compounds 601-630

Table 12

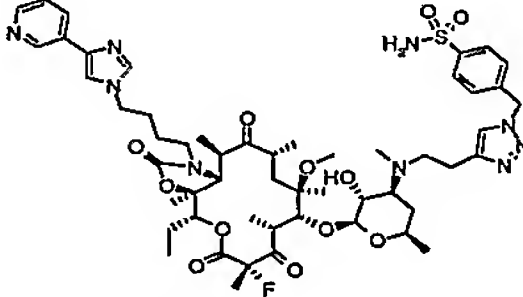
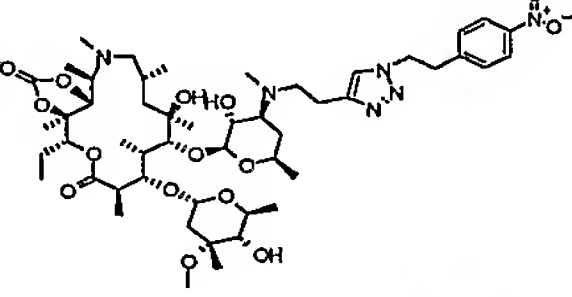
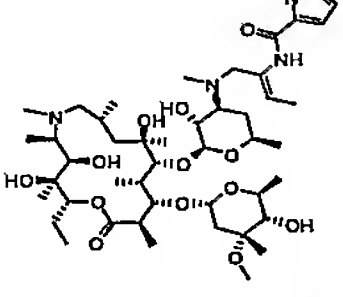
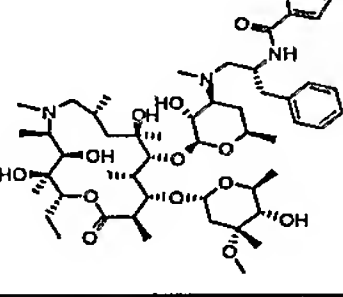
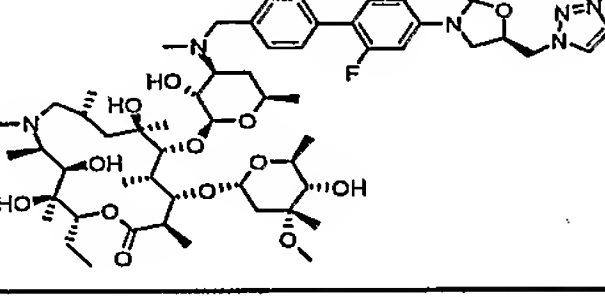
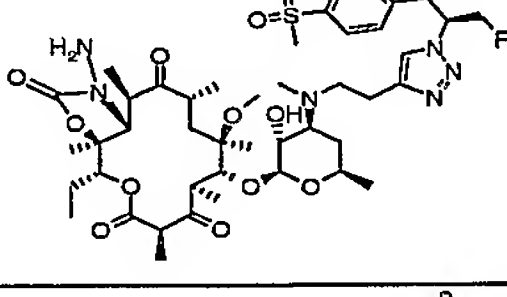
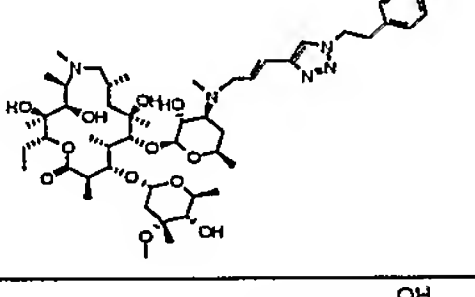
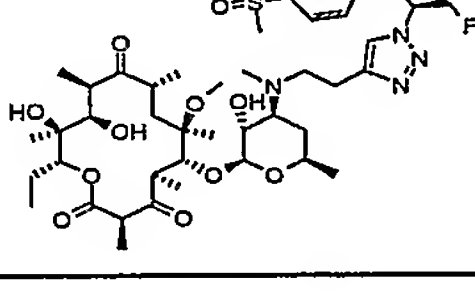
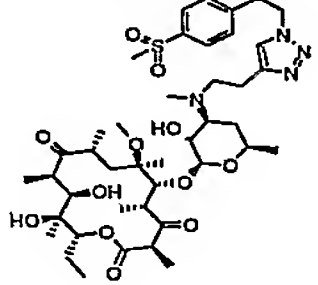
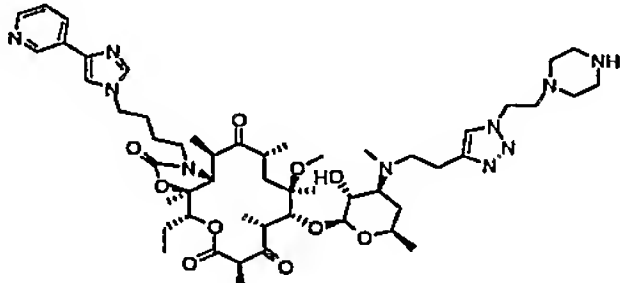
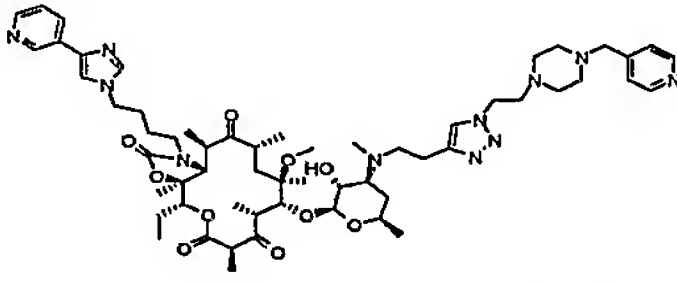
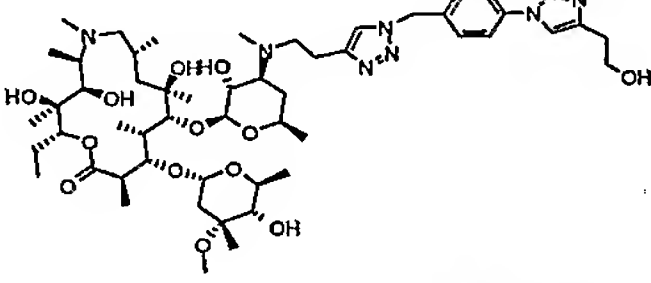
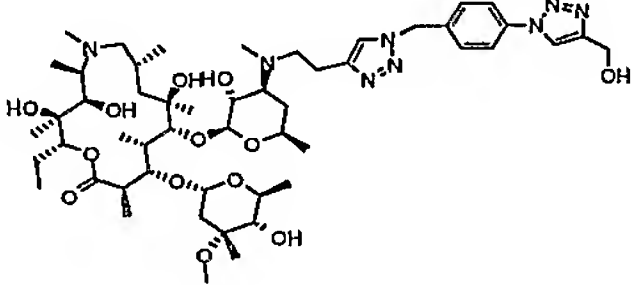
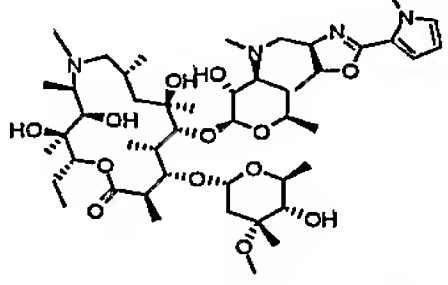
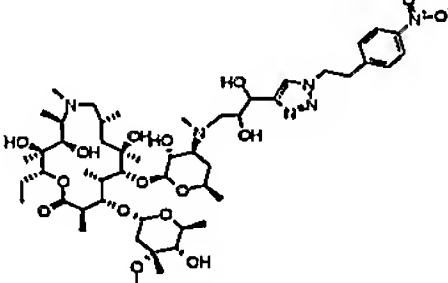
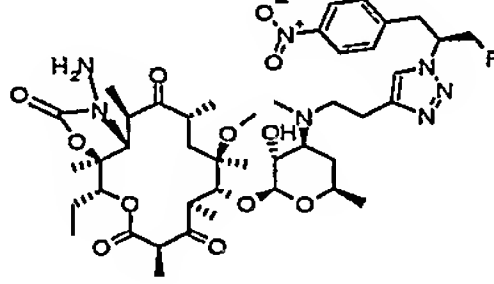
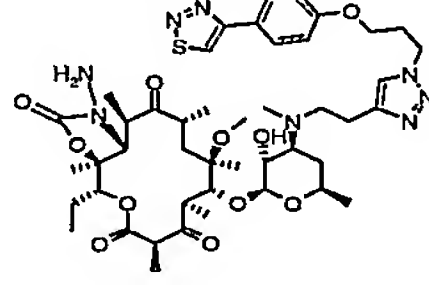
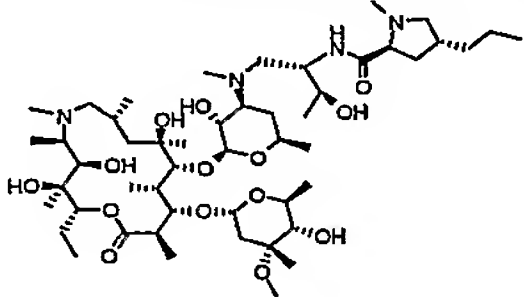
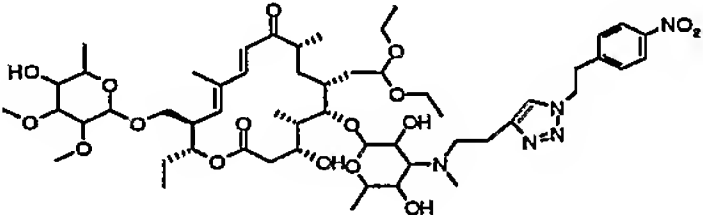
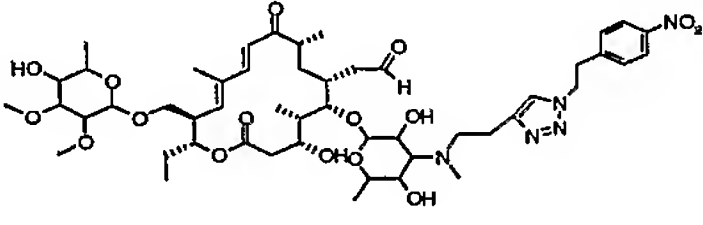
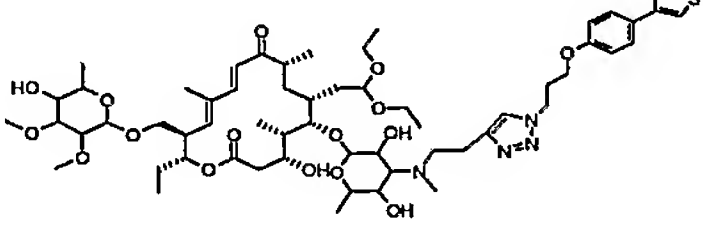
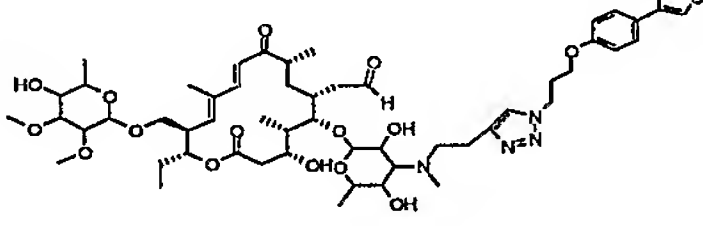
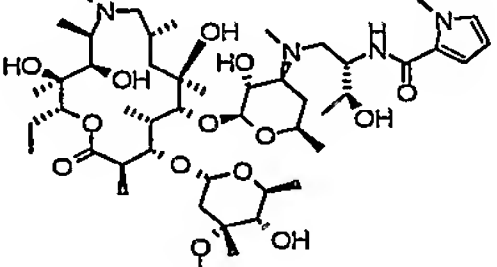
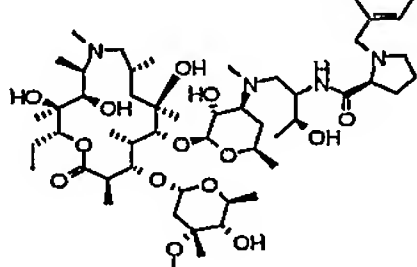
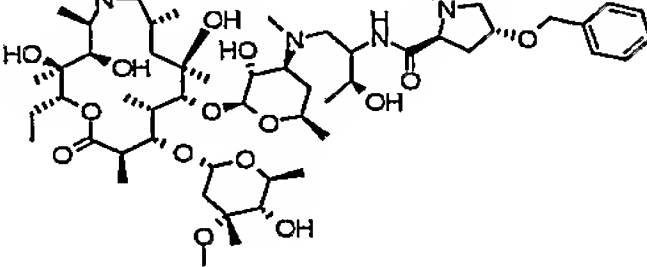
Structure	cpd_number	LCMS M/Z
	601	541.1 (M + 2H) ²⁺
	602	513.2 (M + 2H) ²⁺
	603	456.5 (M + 2H) ²⁺
	604	488.6 (M + 2H) ²⁺
	609	1086 (M + H) ⁺ 544 (M + 2H) ²⁺
	610	940 (M + H) ⁺
	611	497.1 (M + 2H) ²⁺
	612	899 (M + H) ⁺

Table 12 continued

Structure	cpd number	LCMS M/Z
	613	851 (M + H) ⁺
	614	503.4 (M + 2H) ²⁺
	615	1097 (M + H) ⁺
	616	1031.5 (M + H) ⁺
	617	1017.4 (M + H) ⁺
	618	456.1 (M + 2H) ²⁺
	619	513.5 (M + 2H) ²⁺
	620	890 (M + H) ⁺
	621	927 (M + H) ⁺

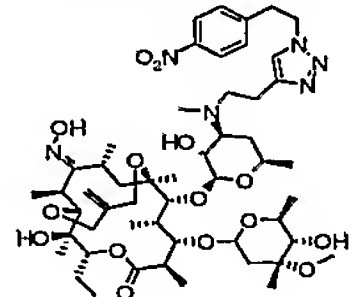
- 265 -

Table 12 continued

Structure	cpd number	LCMS M/Z
	622	975.8 (M + H) ⁺ 447.8 (M + 2H) ²⁺
	623	1076 (M + H) ⁺
	624	1003 (M + H) ⁺
	625	1145 (M + H) ⁺
	626	1072 (M + H) ⁺
	627	929.8 (M + H) ⁺ 465.5 (M + 2H) ²⁺
	628	506.6 (M + 2H) ²⁺
	629	1040 (M + H) ⁺ 520.4 (M + 2H) ²⁺

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Table 12 continued

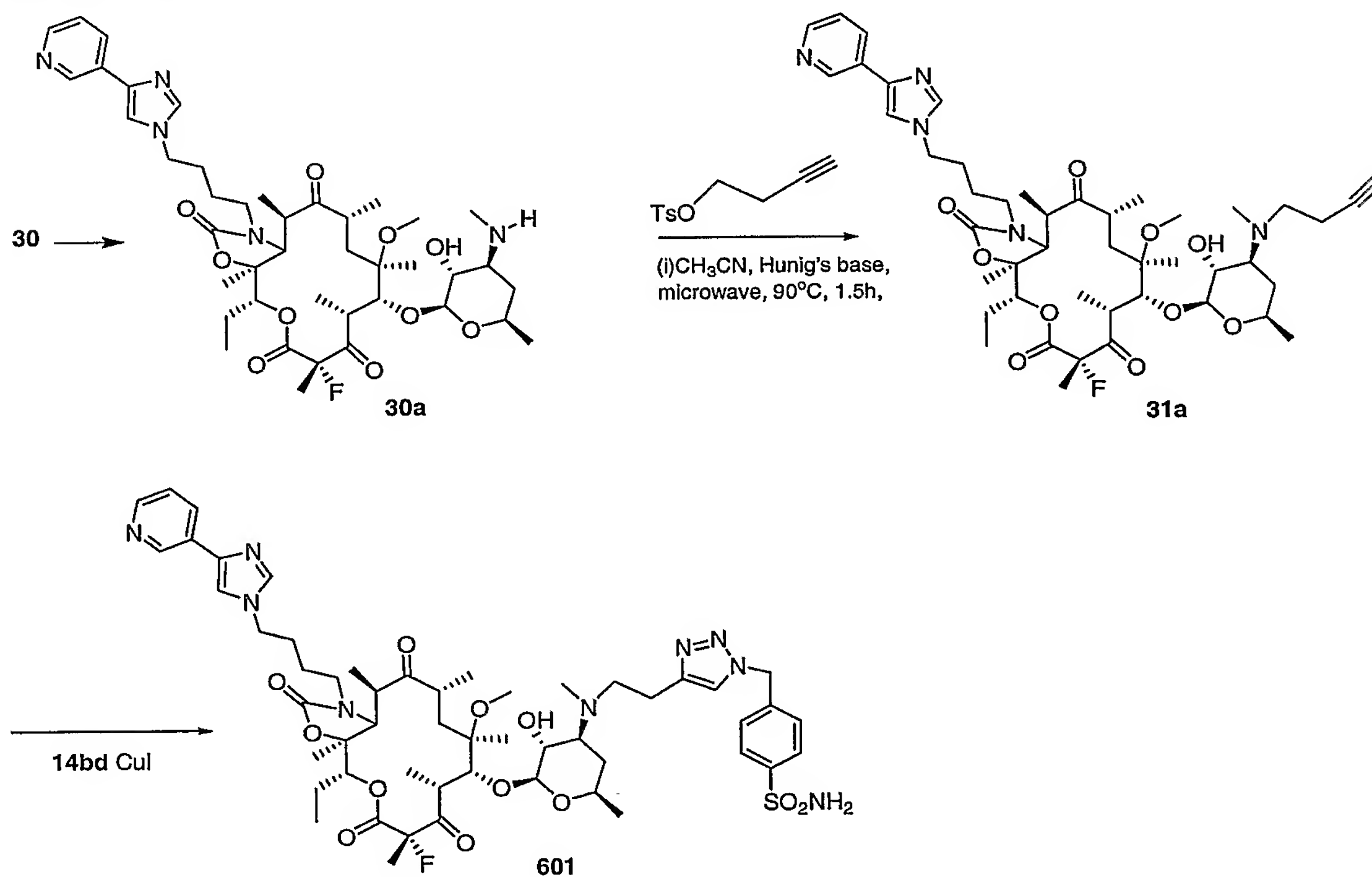
Structure	cpd number	LCMS M/Z
	630	1031 (M + H) ⁺

Synthesis of compound 601

- 5 Compound **601** was synthesized as shown in Scheme 152. Amine **30** of Example 3 was treated according to the procedures of US Patent No. 6,124,269 to afford the 2-fluoro amine **30a**. This was then alkylated with tosylate **11** under the conditions of Example 3 to afford fluoro-alkyne **31a**. This compound was treated with azide **14bd** using the procedures of Example 1 to yield compound **601**.

10

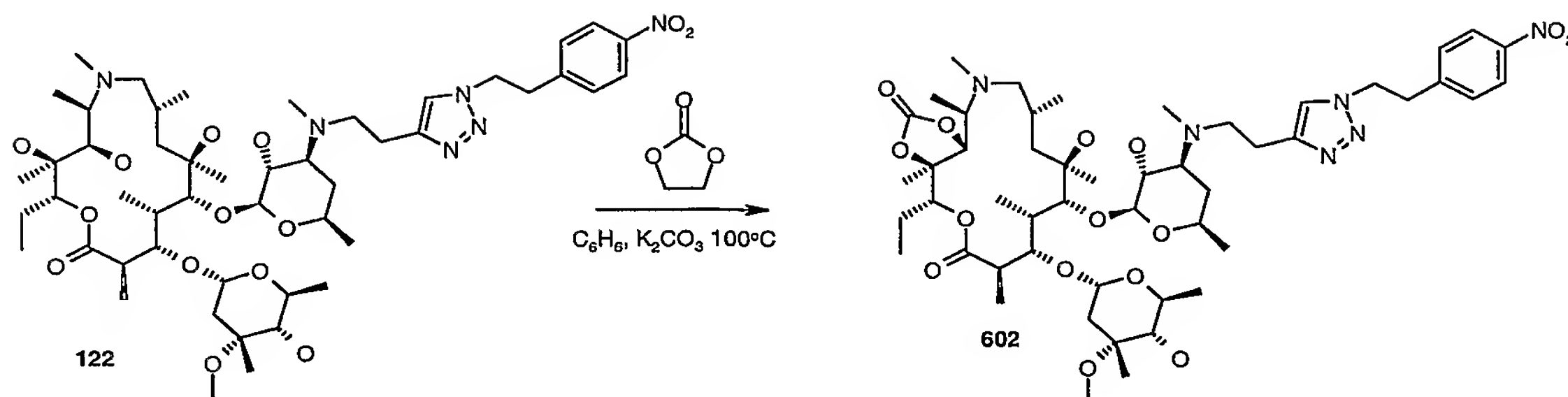
Scheme 152



Compound **602** was synthesized from compound **122** of Example 1 and ethylene carbonate as shown in Scheme 153.

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Scheme 153

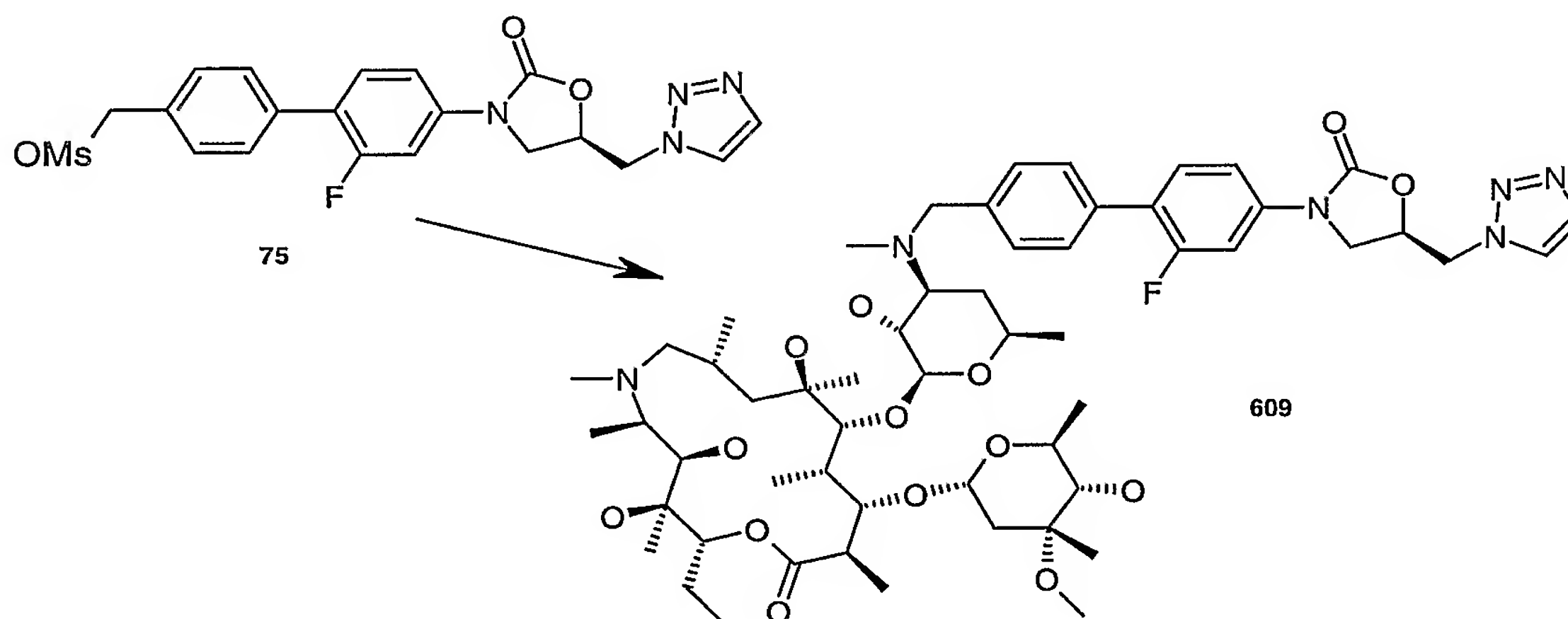
**Synthesis of compound 602**

5 To a solution of **122** (0.1g, 0.1 mmol) in benzene (5 mL) was added K_2CO_3 (0.2g) and ethylene carbonate. The mixture was heated to reflux for 16h then partitioned between water and ether. The ether layer was dried (K_2CO_3), filtered and concentrated to give 0.28g of an oily residue which was purified by silica gel chromatography (elution with 2% methanolic ammonia (2M NH_3) in CH_2Cl_2 to give 0.1g of **601** as a white solid. MS (ESI) m/e 513.2 ($\text{M} + 2\text{H}$)²⁺.

10

Synthesis of compound 609

Scheme 154



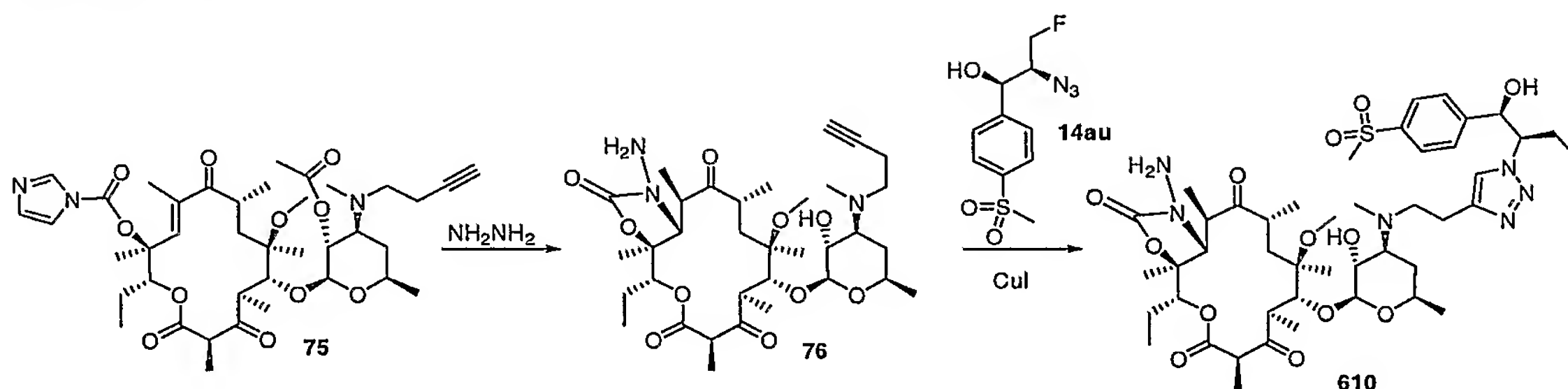
15 A solution *N*- desmethylazithromycin **2** (0.1 g, 0.136 mmol), mesylate **75** (0.067 g, 0.15 mmol) and Hunig's base (1 mL) in DMF (1 mL) was heated to 70°C for 12h. The reaction mixture was concentrated and purified by flash chromatography over silica gel (CH_2Cl_2 -MeOH-

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$\text{NH}_4\text{OH} = 20 : 1 : 0.05$) to gave 0.055 g (38%) of **609**. MS (ESI) m/z 1086 ($\text{M}+\text{H}$)⁺, 544 ($\text{M}+2\text{H}$)⁺.

Synthesis of compound 610

5 Scheme 155



A solution of acylimidazole **75** (0.74 g, 1.0 mmol) in acetonitrile (20 mL) and H_2O (3 mL) was treated with hydrazine monohydrate (0.50 mL, 10 mmol) and stirred at 50 °C for 1 h. The reaction mixture was evaporated to yellow foam and redissolved in methanol (50 mL) and
 10 heated to reflux for 20 h. Solvent was evaporated purification by flash chromatography (SiO_2 , 50–100% ethyl acetate/hexanes) provide the alkyne carbazate **76** (0.50 g, 0.75 mmol) as a white powder.

A solution of **76** (0.10 g, 0.15 mmol) in tetrahydrofuran (3.0 mL) was treated with azide **14au** (62 mg, 0.22 mmol), diisopropylethylamine (0.080 mL, 0.46 mmol), and copper (I) iodide
 15 (8.0 mg, 0.042 mmol) and stirred at 23 °C for 24 h. The reaction mixture was diluted with ammonium hydroxide (30 mL) and extracted with dichloromethane (3×30 mL), dried (Na_2SO_4), and evaporated. Preparative thin-layer chromatography (SiO_2 , 10% methanol/dichloromethane, then ethyl acetate) provided **610** (98 mg, 0.10 mmol) as a white solid: LCMS (ESI) m/e 940 ($\text{M}+\text{H}$)⁺.

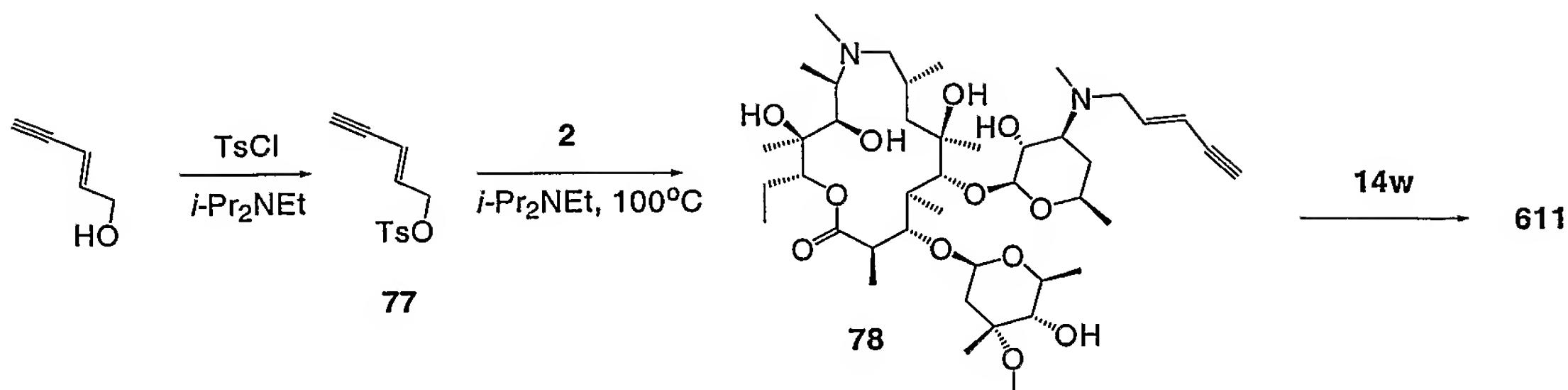
20

Synthesis of compound 611

Scheme 156 illustrates the synthesis of triazole **611**. 2-Penten-4-yn-1-ol was converted to tosylate **77** which was used to alkylate amine **2** to yield enyne **78**. The cycloaddition of alkyne **78** with azide **14w** gave the triazole product **611**.

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Scheme 156

**Synthesis of tosylate 77**

5 To a stirred ice-cold solution of 2-penten-4-yn-1-ol (0.821 g, 10 mmol) in ether (25 mL) was added *p*-toluenesulfonyl chloride (2.0 g, 10.5 mmol). Powdered KOH (1.0 g, 17.8 mmol) was then added portionwise over 5 minutes. The slurry was stirred at 0°C for 45 minutes. The reaction mixture was poured into 100 mL water, and extracted with ether (2 x 50 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , filtered, and concentrated to afford 77 as a yellow oil (2.1 g, 89% yield). Data for 77: ^1H NMR (300 MHz, CDCl_3): δ 7.80 (d, $J = 8$ Hz, 2H), 7.35 (d, $J = 8$ Hz, 2H), 6.12 (dt, $J = 16, 6$ Hz, 1H), 5.70 (ddd, $J = 16, 2, 2$ Hz, 1H), 4.60-4.50 (m, 2H), 2.95 (d, $J = 2$, Hz 1H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 145.1, 135.9, 132.9, 130.0, 127.9, 113.9, 80.3, 79.8, 69.0, 21.66.

Synthesis of enyne 78

15 A 20 mL vial was charged with tosylate 77 (0.20 g, 0.85 mmol), *N*-desmethyl azithromycin $\mathbf{2}$ (0.5g, 0.68 mmol), and Hunig's base (10 mL) then purged with argon gas and sealed. The solution was stirred in a 100°C oil bath for 1h. After cooling to room temperature, the reaction mixture was poured into saturated aqueous NaHCO_3 (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried over K_2CO_3 , filtered, and concentrated to afford 0.72 g of a viscous yellow oil. Purification by silica gel flash chromatography (25 mm x 6" column eluted with 50:1 $\text{CH}_2\text{Cl}_2/2\text{N NH}_3$ in MeOH) gave 78 as a yellow solid (0.48 g, 88% yield). Data for 78: MS (ESI) m/e 400.2 ($\text{M}+2\text{H}$) $^{2+}$, 799.3 ($\text{M}+\text{H}$) $^+$, 821.2 ($\text{M}+\text{Na}$) $^+$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 8.00 (bs, 1H), 6.20 (dt, $J = 16, 7$, Hz, 1H), 5.70-5.60 (m, 1H), 5.00 (d, $J = 4$ Hz, 1H), 4.65 (m, 1H), 4.48 (d, $J = 7$ Hz, 1H), 4.28 (dd, $J = 6, 2$ Hz, 1H), 4.15-3.99 (m, 1H), 3.82 (d, $J = 6$ Hz, 1H), 3.65 (d, $J = 7$ Hz, 1H), 3.60-3.40 (m, 1H), 3.32 (s, 3H), 3.32-3.20 (m, 2H), 2.32 (s, 3H), 2.26 (s, 3H), 0.86 (m, 6H); ^{13}C NMR (75

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MHz, CDCl₃): δ 179.3, 144.4, 111.8, 103.8, 96.2, 85.1, 82.6, 79.7, 79.0, 78.5, 77.5, 75.7, 75.3, 74.4, 73.8, 71.9, 71.0, 69.4, 66.5, 65.4, 62.9, 57.0, 50.39, 45.9, 43.4, 42.0, 37.6, 37.5, 35.9, 31.8, 31.2, 28.2, 27.7, 22.8, 22.5, 22.2, 22.0, 19.3, 17.1, 16.3, 12.1, 10.3, 8.6.

5 Synthesis of triazole **611**

To a stirred solution of **78** (20 mg, 25 μ mol) in THF (100 μ L) was added Hunig's base (20 μ L), azide **14au** (16 mg, 50 μ mol), and cuprous iodide (2.4 mg, 13 μ mol). The resulting mixture was degassed by alternately applying vacuum and purging with argon gas. The slurry was stirred under argon at ambient temperature for 4 h. The entire reaction mixture was then placed atop a silica gel flash chromatography column and eluted with 50:1 CH₂Cl₂/2N NH₃ in MeOH to afford triazole **611** as a white solid (14 mg, 50% yield). Data for **611**: MS (ESI) m/e 496.8 (M+2H)²⁺, 992.3 (M+H)⁺.

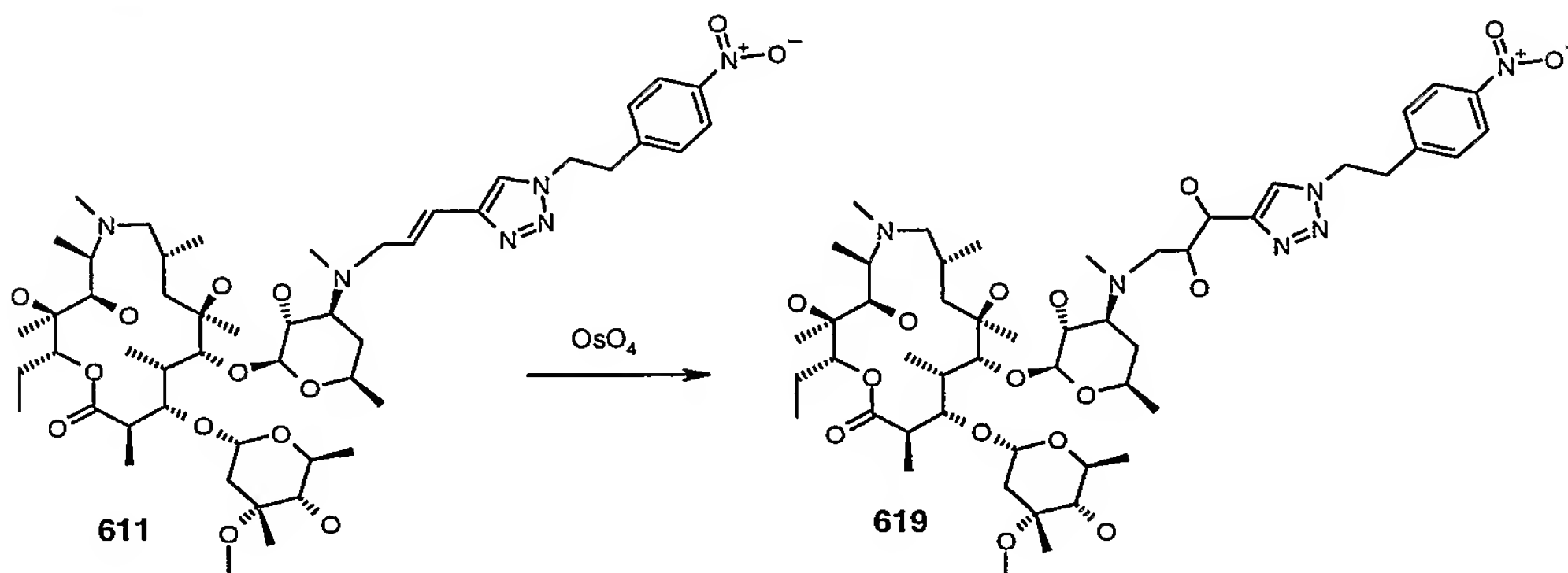
Synthesis of compound **612**

Compound **612** was synthesized from alkyne **27d** of Example 4 and azide **14au** of Table 11 using the copper catalyzed cycloaddition conditions of Example 1.

Synthesis of compound **613**

Compound **612** was synthesized from alkyne **27d** of Example 4 and azide **14b** of Table 11 using the copper catalyzed cycloaddition conditions of Example 1.

Synthesis of **619**:



To a solution of alkene **611** (0.05g, 0.0504 mmol) in acetone (1.5 mL) - H₂O (0.2 mL) was added a solution of *N*-Methylmorpholine *N*-oxide in water (0.013 mL, 50% in H₂O)

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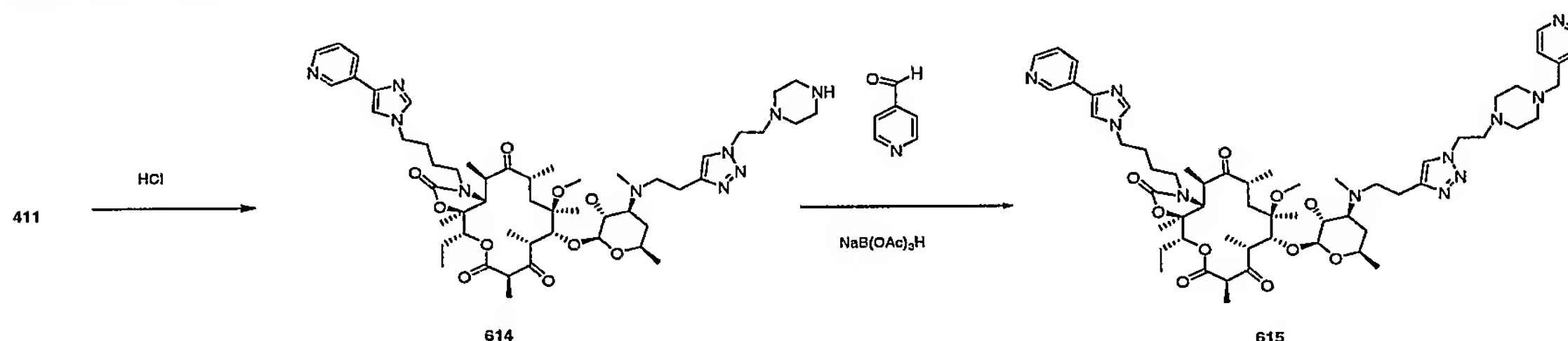
followed by solution of OsO₄ in tertiary-butanol (0.005 mmol, 0.1 M in Bu^tOH). The resulting solution was stirred at ambient temperature overnight and diluted with CH₂Cl₂ (50 mL) and brine (50 mL). The organic layer was separated and washed with brine (2 x 50 mL), dried (anhydrous Na₂SO₄), concentrated and purified by preparative TLC (CH₂Cl₂ : 2% NH₃-MeOH = 13 : 1).

5 Yield: 20 mg (40%). MS (ESI) *m/z* 1026 (M+H)⁺, 513.5 (M+2H)⁺.

Synthesis of compounds 614 and 615

Compound **614** was synthesized from compound **411** of Example 3 by treatment with hydrochloric acid. Compound **615** was synthesized from **614** by reductive alkylation with
10 pyridine-4-carboxaldehyde as shown in Scheme 158.

Scheme 158



To a solution of 0.015 g (0.015 mmol) of **614**, 0.006 g (0.060 mmol) of pyridine 4-carboxaldehyde in 1.0 ml of DMF was added 0.007 g (0.030 mmol) of NaBH(OAc)₃. The
15 reaction mixture was allowed to stir at 25 °C for 4 h, DMF was removed by rotary evaporation, and the residue was purified through preparative TLC to give 0.003 g of compound **615**. MS (M+1): 1097.

20 Synthesis of compound 616

This compound was synthesized by heating a mixture of mesylate **82** (0.18 g, 0.46 mmol) and amine **2** (0.43 g, 0.55 mmol) in DMF (6 mL) and Hunig's was heated under reflux for 20h. Solvent was evaporated off. The crude residue after solvent evaporation was suspended in CH₂Cl₂ (50 mL) and extracted with saturated NaHCO₃ (2 x 30 mL) and saturated brine (1 x 30
25 mL). The organic layer was decolorized with decolorizing charcoal and dried over Na₂SO₄. Solvent was evaporated off and the crude was purified on silica gel column, eluting with CH₂Cl₂/MeOH/H₂O 14:1:0.05 to 12:1:0.05 to 10:1:0.05 to give **616** (0.048 g, 10 %) as a white solid. LC-MS; M+H⁺ 1031.5

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Synthesis of compound 82:

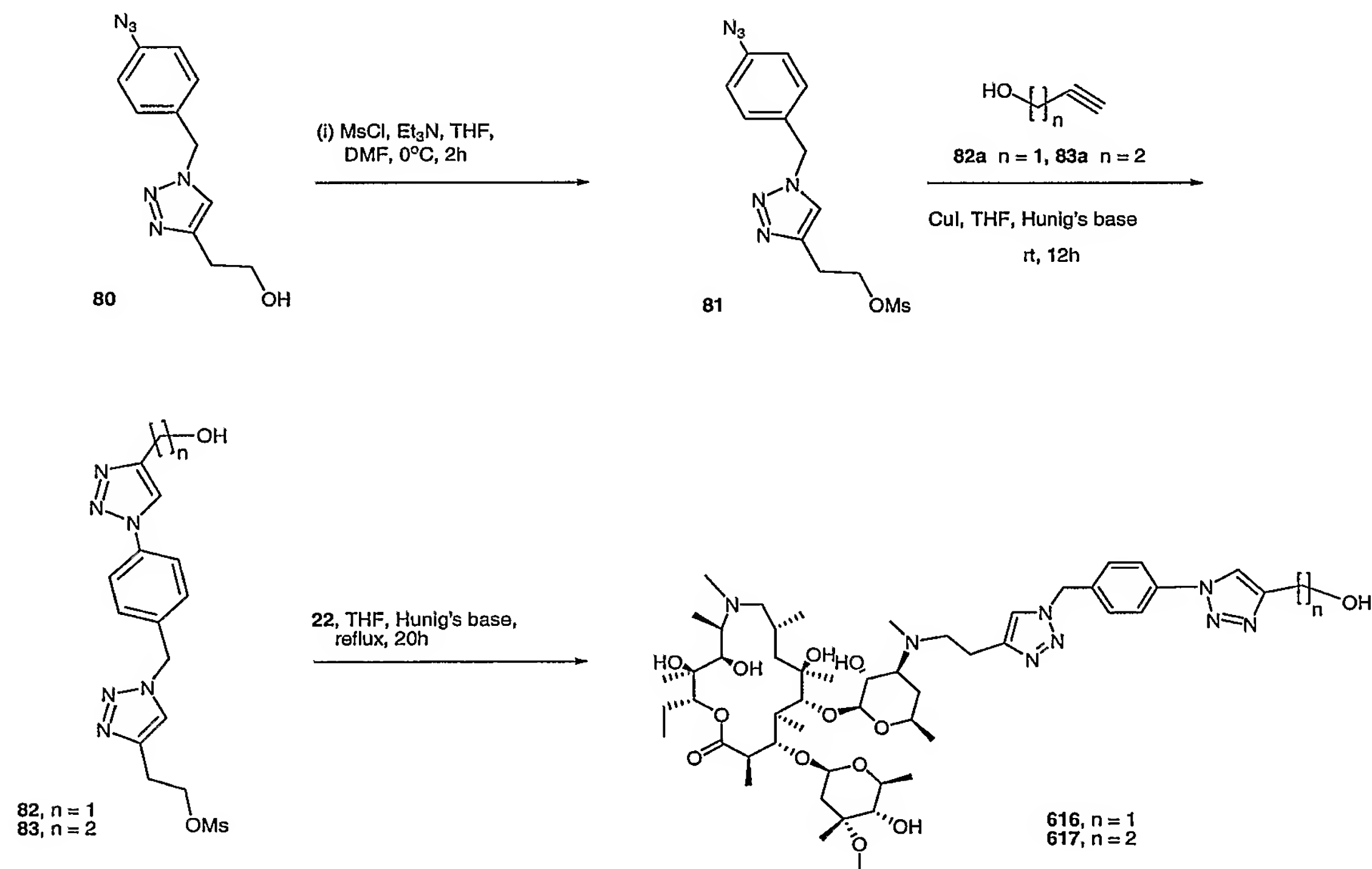
Alcohol **80** was converted to the mesylate derivative **81** (LC-MS; $M+H^+$ 322.9).

Compound **81** (0.39 g, 1.21 mmol) was reacted with alkyne **82a** (0.13 mL, 2.22 mmol) in the presence of CuI (0.183 g, 0.96 mmol) in THF (10 mL) and Hunig's base (1 mL) mixture at room temperature within 12h. The reaction was partitioned between saturated ammonium chloride (30 mL) and EtOAc (40 mL). The aqueous layer was extracted with EtOAc (4 x 20 mL) and the combine organic layer was dried over Na_2SO_4 . Solvent was evaporated and the crude was purified on silica gel, eluting with CH_2Cl_2 / MeOH 19:1 to 17:1 to furnish alcohol **82** as a white solid (0.171 g, 37 %). LC-MS; $M+H^+$ 378.8

Synthesis of compound 83.

This compound was synthesized from compound **80** and alkyne **83a** as described for the synthesis of **82** except that the crude **83** was used without further purification (90 % yield, whitish-yellow solid). LC-MS; $M+H^+$ 392.9.

Scheme 159



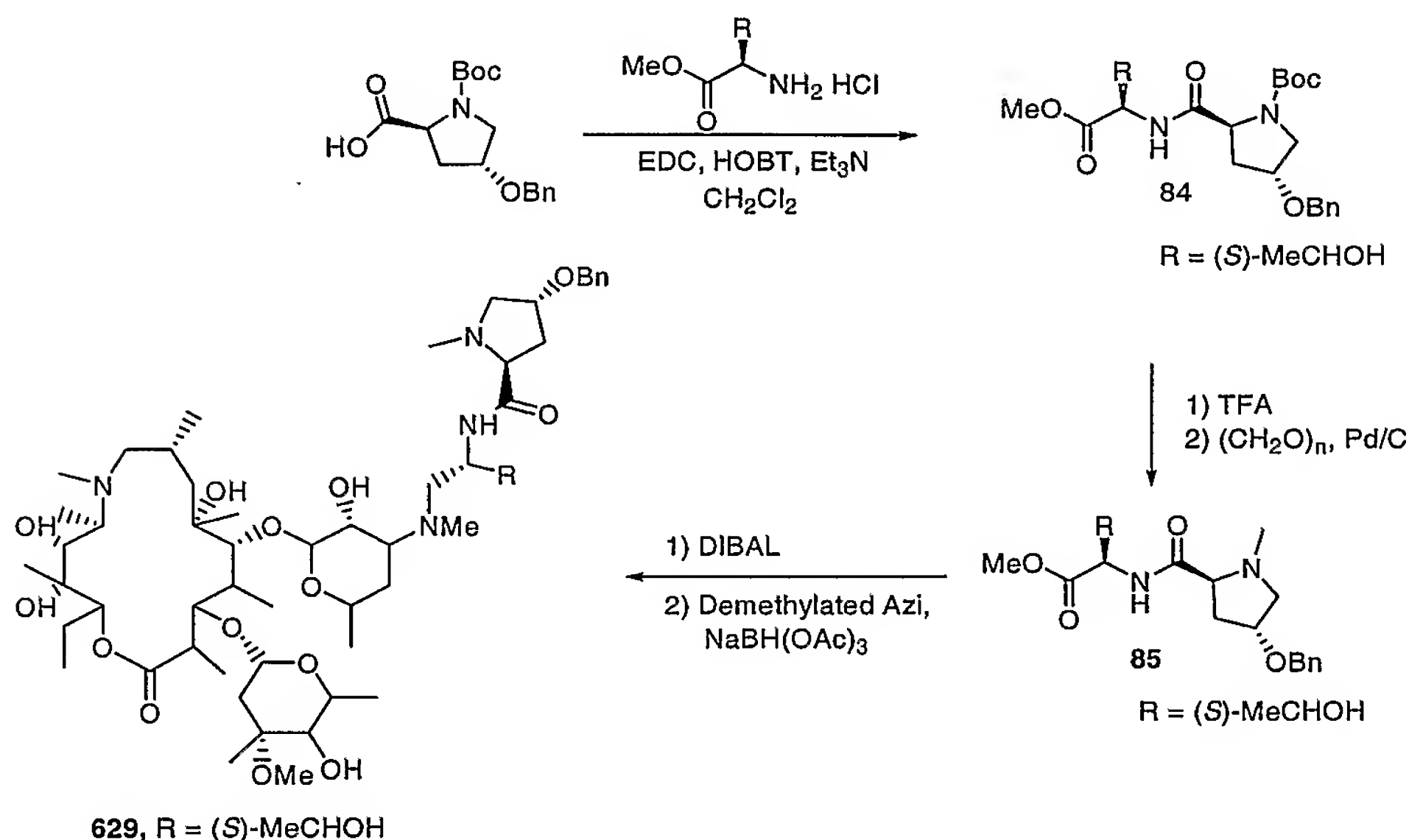
- 273 -

Synthesis of compound 617.

This compound was synthesized by heating a mixture of alcohol **83** (0.14 g, 0.37 mmol) and amine **2** (0.346 g, 0.44 mmol) in DMF (4 mL) and Hunig's base (2 mL) at 110°C for 24h. Solvent was evaporated off and the crude was purified on silica gel column, eluting with CH₂Cl₂/MeOH/NH₄OH 20:1:0.05 to 18:1:0.05 to 15:1:0.05 to give **617** (0.173 g, 46 %) as a white solid. LC-MS; M+H⁺ 1017.4.

Synthesis of compound 629

Scheme 160

**Synthesis of 84**

To a stirred solution of Boc-Hyp(Bz)-OH (321.4 mg, 1.0 mmol), Thr-OMe hydrochloride (155.6 mg, 1.0 mmol), EDC (249.2 mg, 1.3 mmol), and HOBT (202.7 mg, 1.5 mmol) in CH₂Cl₂ was added Et₃N (0.42 mL) at rt. The resulting mixture was stirred at this temperature for 3 hr. Water (10 mL) was added, and the aqueous phase was extracted with CH₂Cl₂ (20 mL x 3). The combined organic phase was washed with brine, and dried over MgSO₄. The concentrated residue was purified on silica gel with gradient elution from 1:9 to 7:3 of EtOAc:Hexanes to provide the dipeptide **84** as a clear oil (374.6 mg, 95%)

Synthesis of 85

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The dipeptide **84** (775.0 mg) prepared above was dissolved in CH₂Cl₂/TFA (5 mL/5 mL). The mixture was stirred at room temperature for 1.5 hr and concentrated to dryness. The solid residue obtained was dissolved in EtOH (70 mL), treated with (CH₂O)_n (514.5 mg, 17.15 mmol), Pd/C (77.5 mg) under hydrogen atmosphere (balloon) overnight. The mixture was
5 filtered. The concentrated filtrate was purified on silica gel with gradient elution from 1:1 to 1:0 of EtOAc:Hexanes to give the *N*-methylated dipeptide **85** as a white solid (320.2 mg, 53%).

Synthesis of **629**

DIBAL (1.0 M in toluene, 2.61 mL) was added in 10 min. to a stirred solution of the
10 dipeptide **85** (320.2 mg, 1.05 mmol) in toluene at -78 °C. After 2 hr at this temperature, the mixture was quenched by addition of methanol (0.6 mL). The mixture was diluted with EtOAc and then stirred with saturated Rochelle salt (5.2 mL) at 0 °C for 1.5 hr. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine, and dried over MgSO₄.

15 The concentrated residue obtained above was dissolved in 1,2-dichloroethane (10 mL), and treated with demethylated azith **2** (308.7 mg, 0.42 mmol), and NaBH(OAc)₃ (133.5 mg, 0.63 mmol). The mixture was stirred at room temperature for 16 hr. and quenched with saturated NaHCO₃. The organic phase was separated, washed with brine, and dried over MgSO₄. The concentrated residue was purified on silica gel with gradient elution from 0:1 to 15:85 of MeOH:
20 CH₂Cl₂ to provide **629** as a white solid (105.8 mg, 25%).

Synthesis of compounds **603**, **604**, **622**, **627**, and **628**

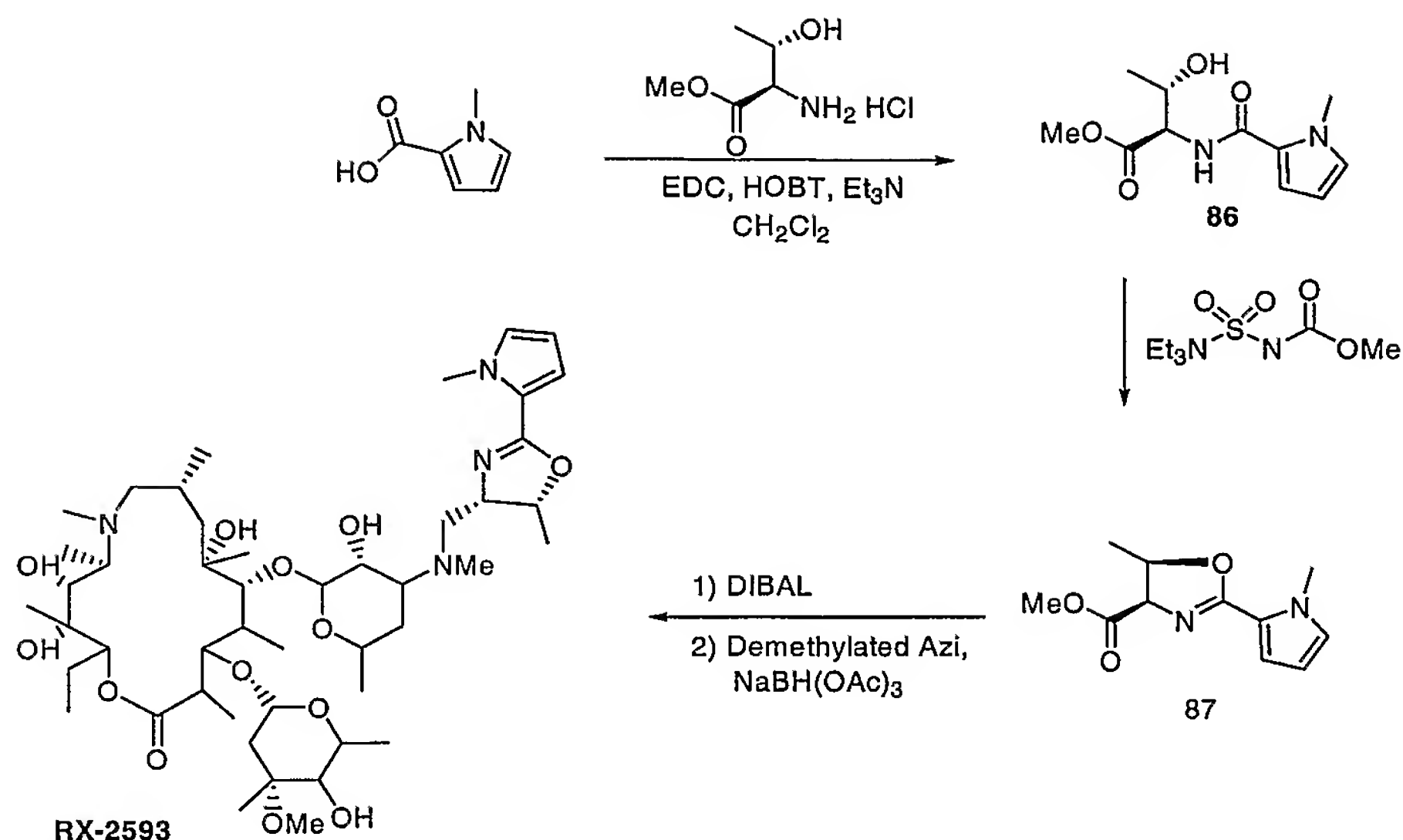
Similar procedures to those described for compound **629** were employed to synthesize compounds **603**, **604**, **622**, **627**, and **628**, all of which contain related dipeptide substituents.

25

Compound **618** was synthesized as shown in scheme 161 below.

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Scheme 161



Synthesis of intermediate 87

5

Dipeptide **86** (495.9 mg, 2.07 mmol) and Burgess reagent (738.6 mg, 3.10 mmol) were dissolved in THF (15 mL). The resulting mixture was refluxed for 3 hr. After the mixture was cooled down, water (10 mL) was added, and the mixture was extracted by EtOAc (30 mL x 3). The combined organic phase was washed with brine and dried over MgSO₄. The concentrated residue was purified on silica gel with gradient elution from 0:1 to 3:7 of EtOAc: Hexanes to provide the dehydrated dipeptide as a light yellow oil (348.1 mg, 76%).

10

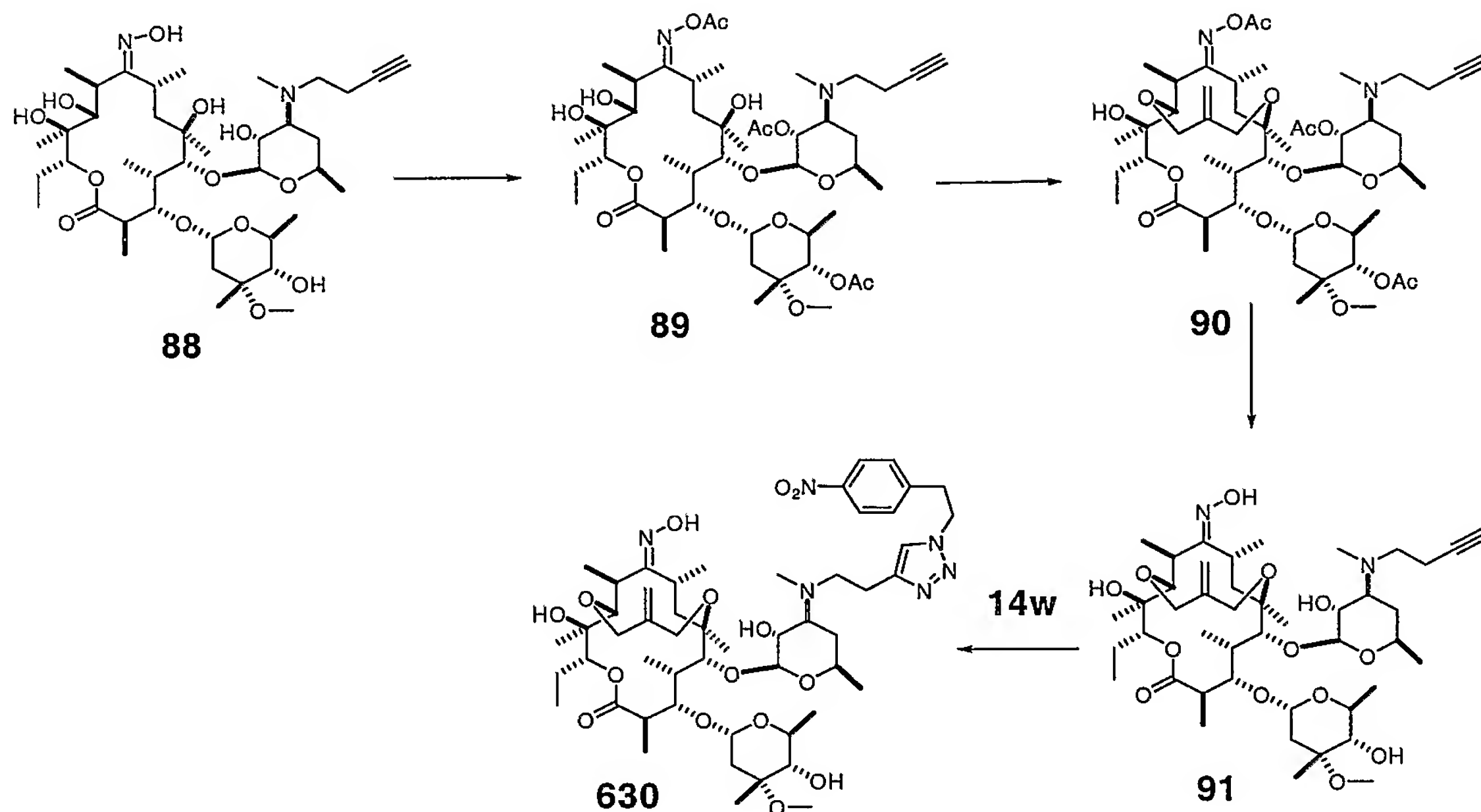
Synthesis of compound 618

This compound was synthesized from intermediate **87** and amine **2** using the conditions described above for the synthesis of compound **629** from intermediate **85**

15

Synthesis of compound 630

Scheme 162

**5 Synthesis of compound 89**

To a solution of compound 88 (2.00g, 2.54mmol) in THF (17mL) at 0°C was added Et₃N (1.50mL, 10.67mmol), followed by addition of acetic anhydride (946μL, 9.91mmol), then, DMAP (34mg, 0.25mmol). The mixture was stirred at 0°C for 3h, then, Et₃N (150μL, 1.07mmol) and acetic anhydride (95μL, 0.99mmol) were added. The mixture was stirred for 3h, then, MeOH (2.0ml) was added. The reaction mixture was concentrated and EtOAc (100mL) was added, washed with saturated NaHCO₃ (30.0mL), then, brine (30.0mL), dried with Na₂SO₄, gave 2.28g **89**. The residue was used for the next step without further purification. MS (ESI) *m/e* 913 (M + H)⁺.

15 Synthesis of compound 90

To a solution of triacetate compound **89** (913mg, 1.00mmol, crude), 2-methylene-1,3-propane-[bis-(tert-butyl)carbonate] (865mg, 3.00mmol) and 1,4-bis(diphenylphosphino)-butane (dppb) (305mg, 0.70mmol) in THF (10mL, degassed) was added Pd₂(dba)₃ (92mg, 0.10mmol) at room temperature. The mixture was refluxed for 12h, then, the reaction mixture was concentrated and EtOAc (100mL) was added. Washed with saturated NaHCO₃ (30mL), brine

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(30mL), dried with Na₂SO₄, The residue was isolated by silica gel chromatography (CH₂Cl₂ to 2% MeOH in CH₂Cl₂ containing 0.2% NH₄OH), gave 340mg of **90** in 35% yield for two steps. MS (ESI) *m/e* 966 (M + H)⁺.

5 **Synthesis of compound 91**

A compound **90** (330mg, 0.34mmol) in MeOH (6mL), was refluxed for 5 days. The residue was isolated by FC (CH₂Cl₂ to 2% MeOH in CH₂Cl₂ containing 0.2% NH₄OH), gave 143mg of **91** in 50% yield.

MS (ESI) *m/e* 839 (M + H)⁺.

10

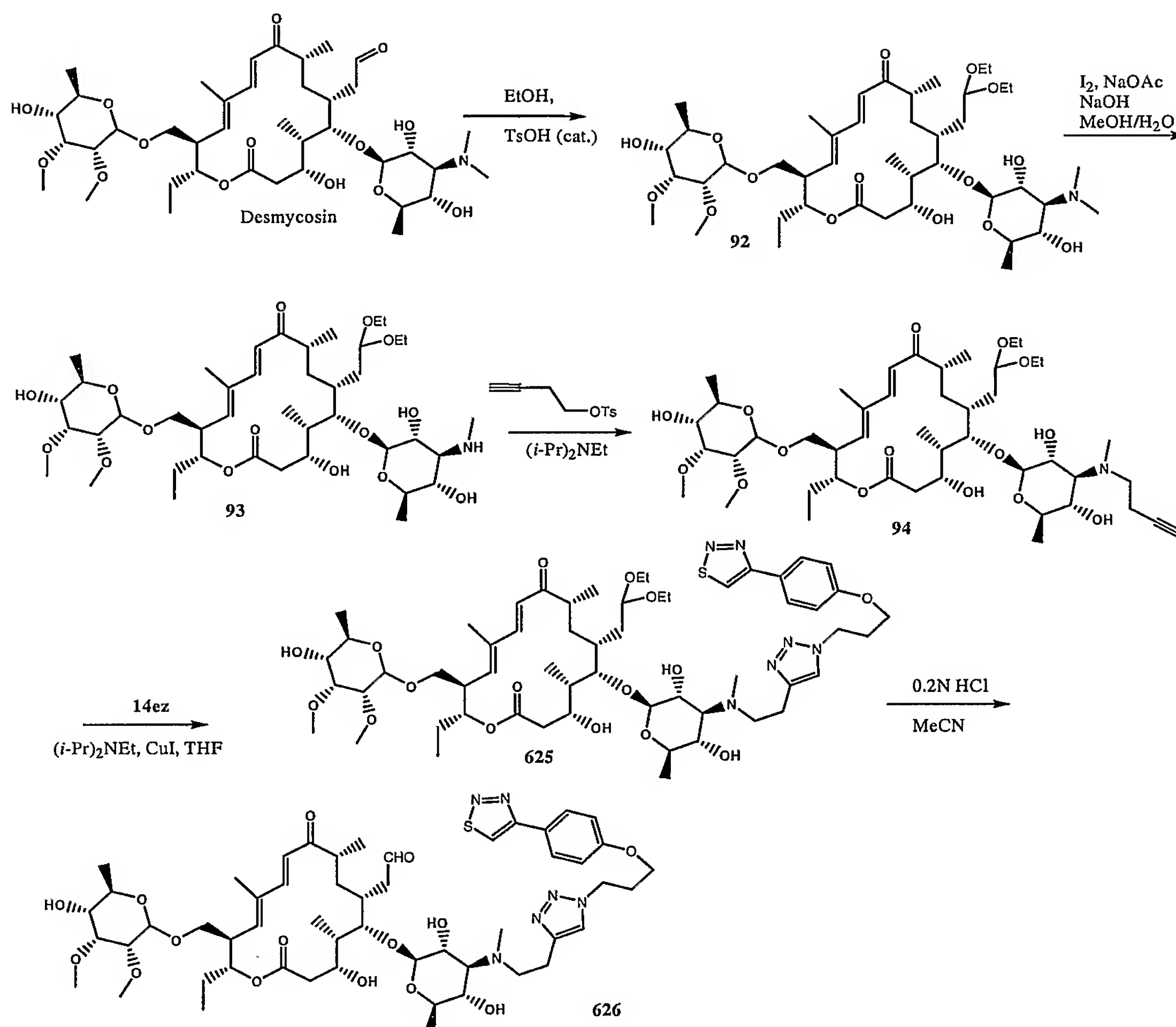
Synthesis of compound 630

A mixture of compound **91** (58mg, 0.07mmol) and azide **14w** (40mg, 0.21mmol), CuI (2mg) and Hunig's base (3 drops) in THF (0.3mL) was stirred at room temperature for 10 hours. The reaction was quenched by addition of NH₄OH (3drops), saturated NH₄Cl (1drop), water (2mL) and CH₂Cl₂ (3mL). After stirring for 20min, the organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (10 mL X 3), and dried with Na₂SO₄, The residue was isolated by FC (2/100/0.2 MeOH/ CH₂Cl₂/NH₄OH), to give 62mg of **630** in 86% yield. MS (ESI) *m/e* 1031 (M +H)⁺.

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Synthesis of compounds 625 and 626

Scheme 163



Synthesis of compound 92

- 5 To a solution of 1.00 g (1.30 mmol) of desmycosin in 10 ml of ethyl alcohol was added 0.260 g (1.36 mmol) of *p*-toluenesulfonic acid at ambient temperature. The reaction mixture was allowed to stir for 3 h, then diluted with 30 mL of saturated aqueous NaHCO₃, and extracted with EtOAc. The combined ethyl acetate extracts were washed with brine, dried over MgSO₄, and concentrated to give 1.220 g of **92** which was used without further purification.

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Synthesis of compound 93

To a mixture of 0.250 g (0.29 mmol) of **92** and 0.486 g (5.92 mmol) of NaOAc in 10 mL of MeOH/H₂O (80% MeOH) at 55 °C was added 0.075 g (0.29 mmol) of solid iodine. The pH value of the reaction mixture was maintained at 9 by addition of 1 N NaOH at time intervals of 10, 30, and 60 minutes after the addition of iodine. The reaction mixture was stirred at 55 °C for 1 h following the last addition of NaOH solution, then diluted with 25 mL of saturated NaHCO₃ and extracted with EtOAc (50 ml x 2). The combined EtOAc extracts were washed sequentially with 15 ml of 5% NaS₂O₄ and brine, dried over MgSO₄, filtered and concentrated to give 0.221 g of **93**.

Synthesis of alkyne 94

A mixture of 0.200 g (0.24 mmol) of **93**, 0.270 g (1.20 mmol) of tosylate **11**, 0.311 g (2.41 mmol) of di-isopropylethylamine and 10 mg of dimethylaminopyridine in 5 ml of THF was allowed to stir at 55 °C for 48 h. The mixture was diluted with 20 ml of saturated NaHCO₃, extracted with EtOAc (30 ml x 3). The combined organic layers were washed with brine (20 ml), dried over MgSO₄, filtered and concentrated to give 0.065 g of desired product **94** and 0.063 g of recovered starting material **93** after purification through flash column chromatography on silica gel.

Synthesis of compound 625

A solution of 0.300 g (0.03 mmol) of alkyne **94**, 0.018 g (0.06 mmol) of azide **14ez** and 0.006 g (0.03 mmol) of CuI in 3.0 ml of THF was degassed, then put under argon. To the mixture was added 4 drops of Hunig's base. The reaction was stirred at 25 °C for 6 h. To it was added 20 mL of 10% NH₄OH, stirred for 10 min, extracted with CH₂Cl₂ (30 mL x 3), combined organic layers were washed with brine, dried, concentrated, purified through preparative TLC to give 0.020 g of the final product. MS (ESI) *m/e* 1145 (M + H)⁺.

Synthesis of compound 626

A solution of 0.015 g (0.013 mmol) of compound **625** in 1.0 ml of 0.2 N HCl and 1.0 mL of acetonitrile was stirred at 25 °C for 4 h. To it was added 15 mL of saturated aqueous NaHCO₃ solution, the aqueous layer was then extracted with CH₂Cl₂ (40 mL x 3), combined

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organic layers were washed with brine, dried, and concentrated to give 0.003 g of pure **626**. MS (ESI) m/e 1172 ($M + H$)⁺.

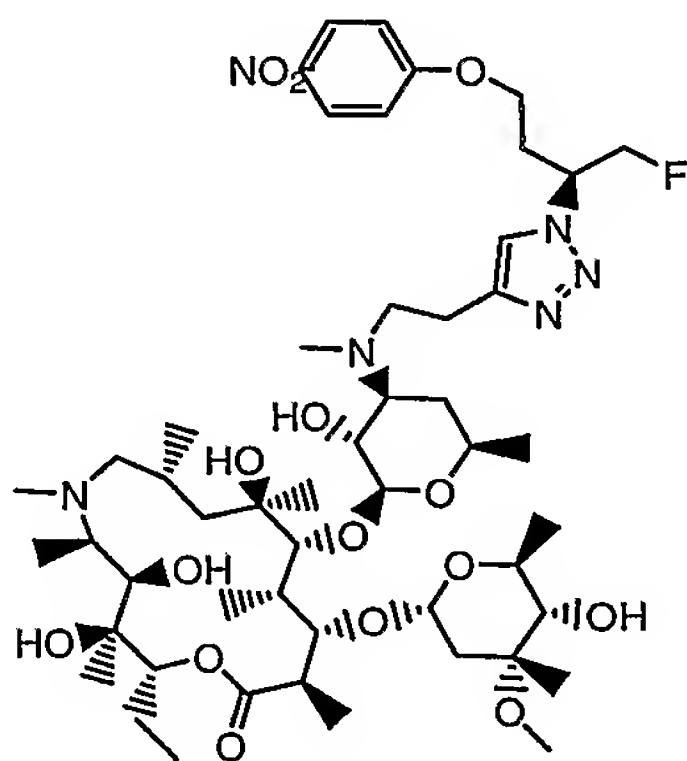
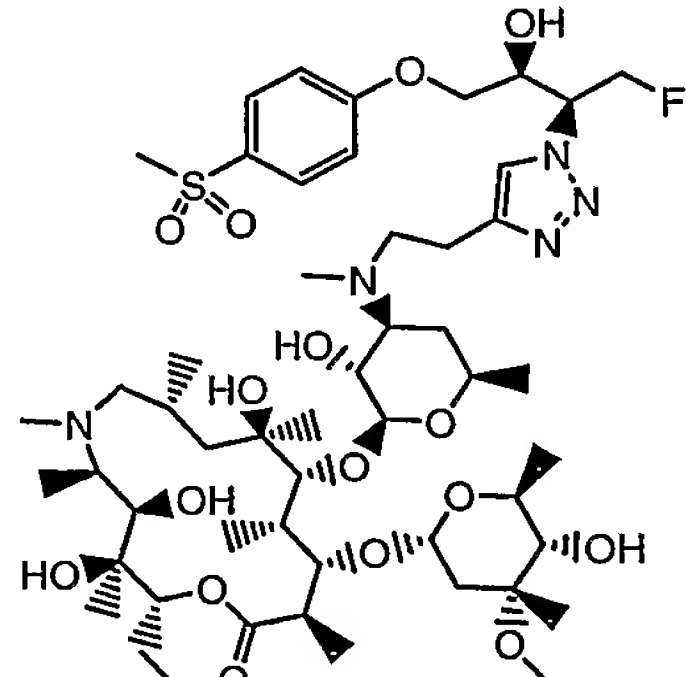
Synthesis of compounds **623** and **624**

5 These compounds were synthesized from intermediate **94** and azide **14w** using the procedures described above for compounds **625** and **626**.

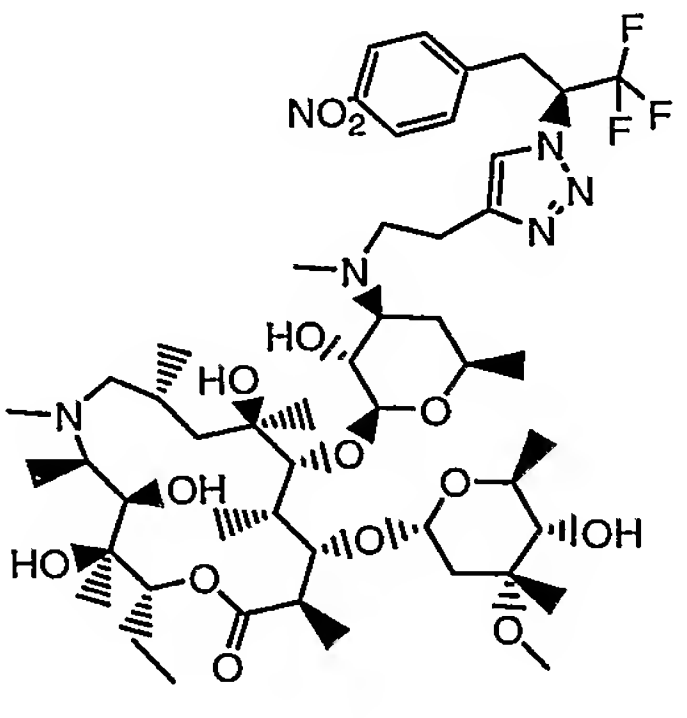
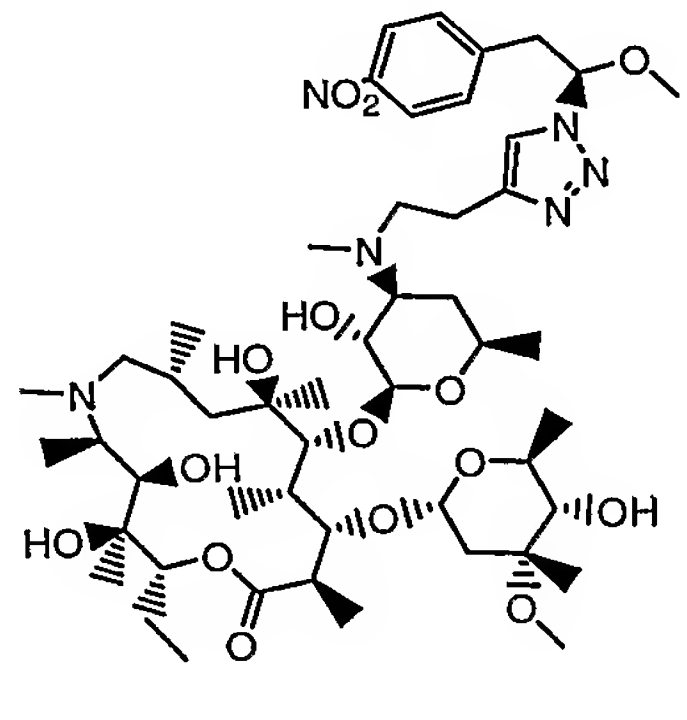
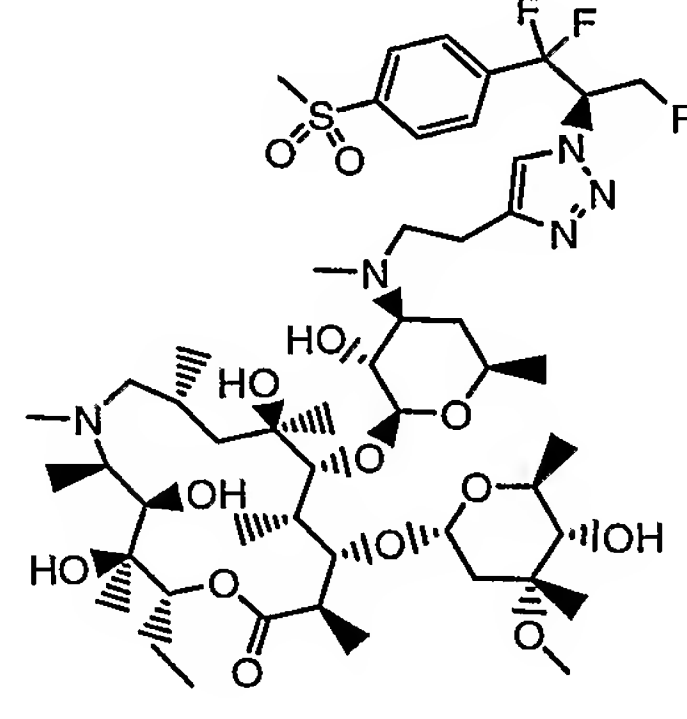
Example 12 compounds **701-756**

10 Additional compounds of the invention are shown in Table 13 below. These compounds are made in accordance with the procedures presented in Examples 1-11 above.

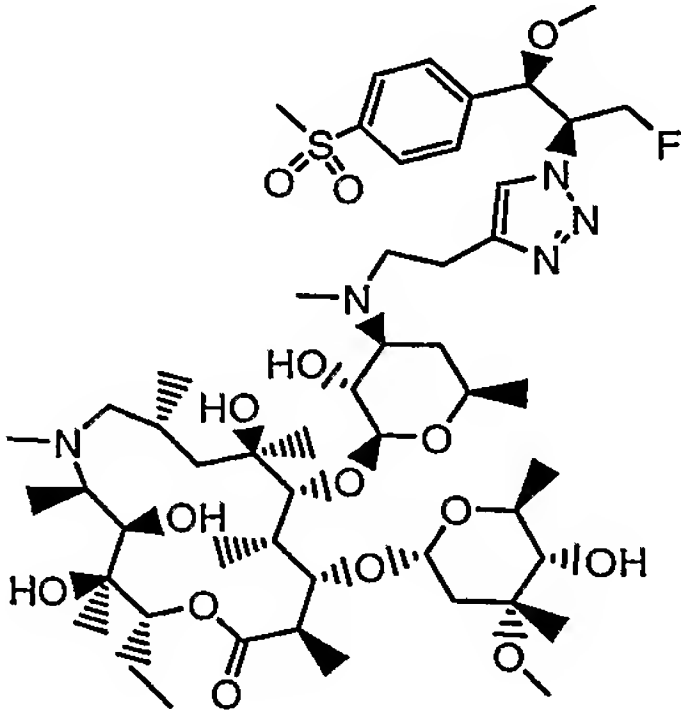
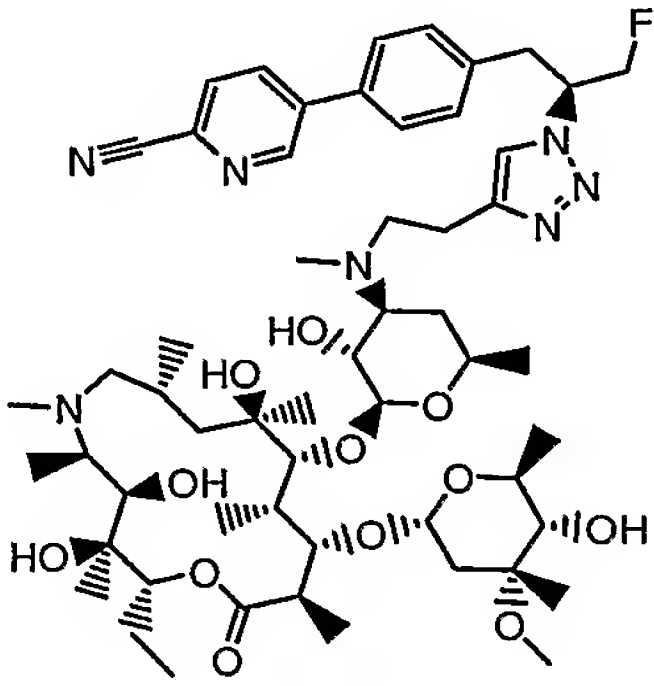
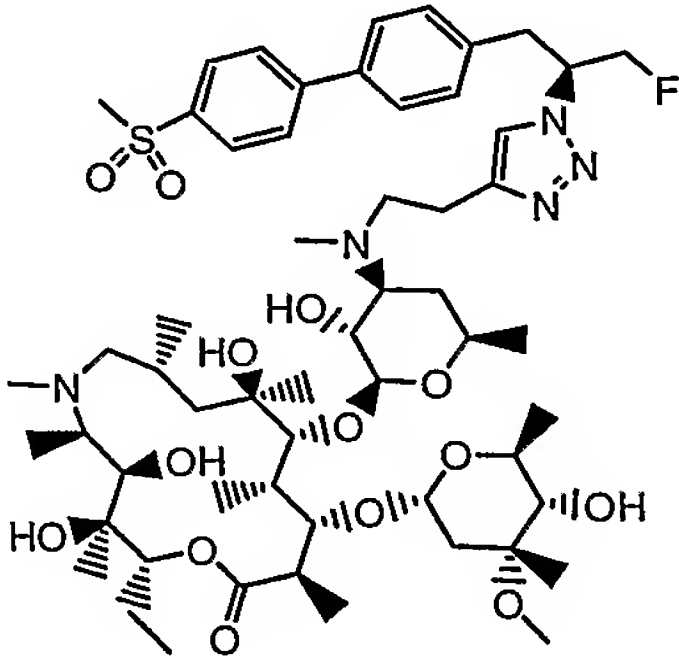
Table 13

Compound Number	Structure
701	
702	

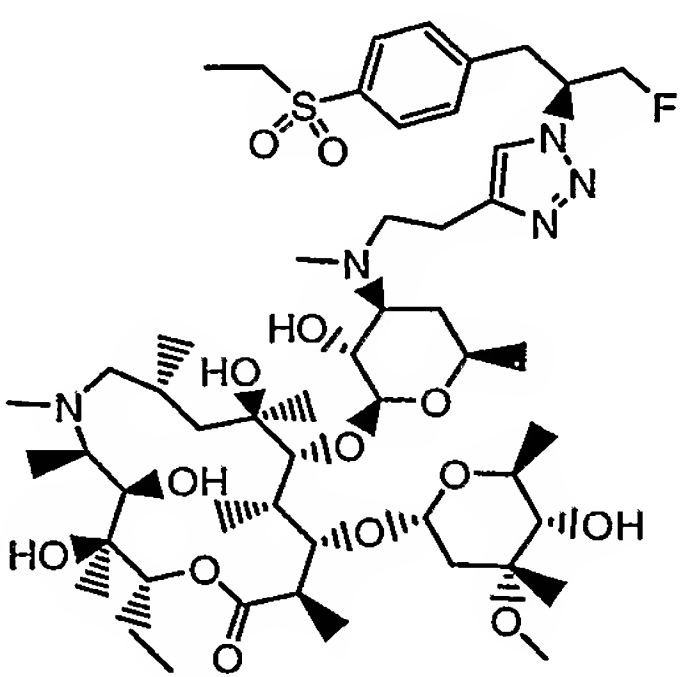
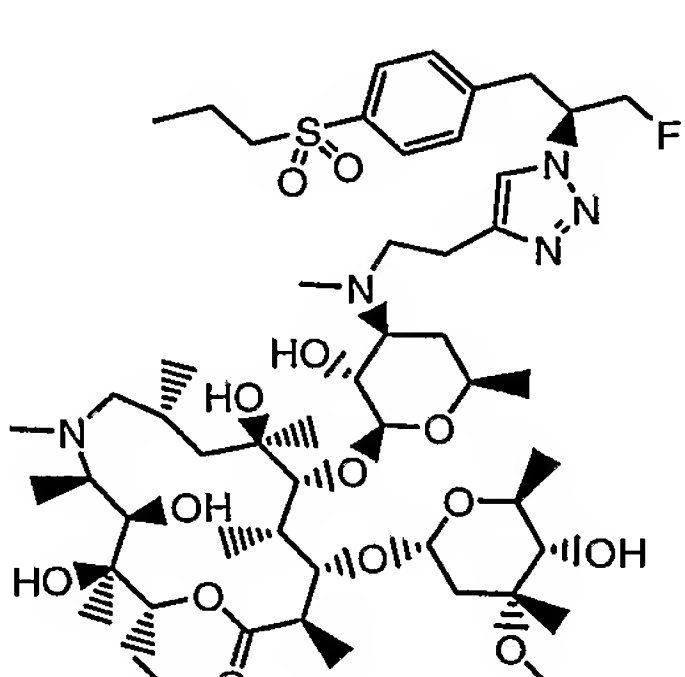
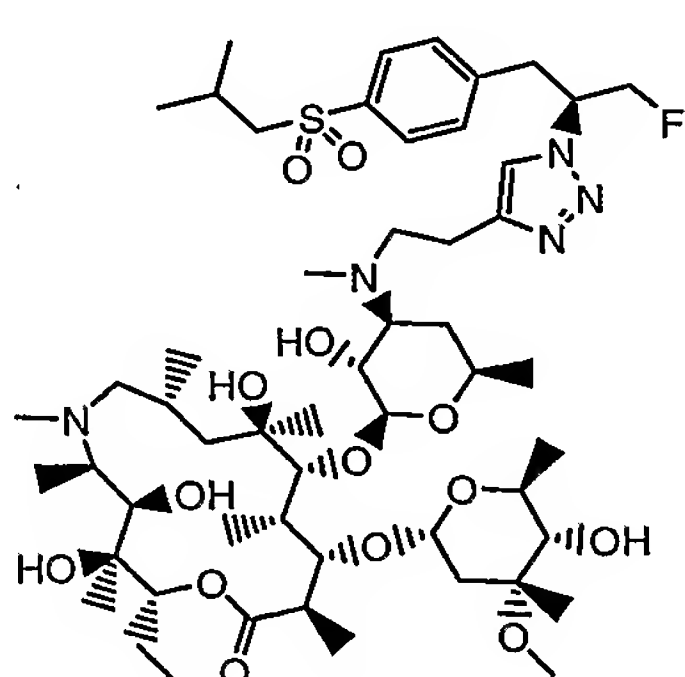
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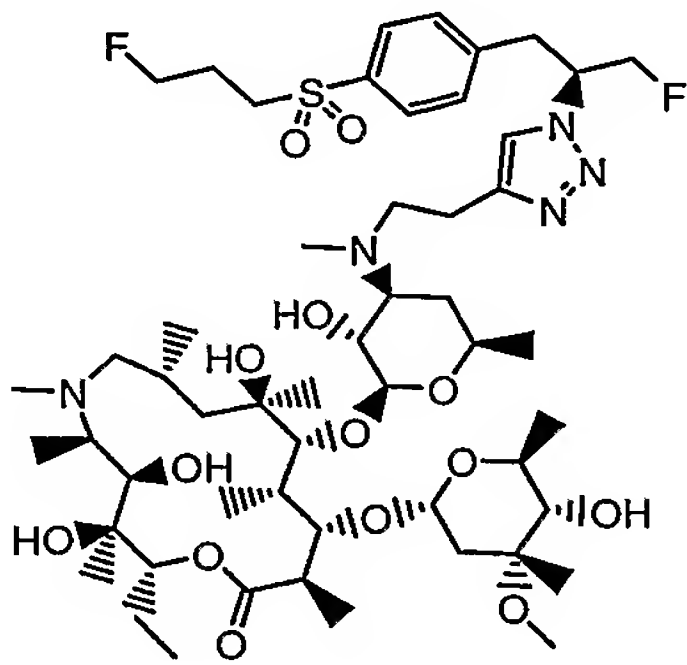
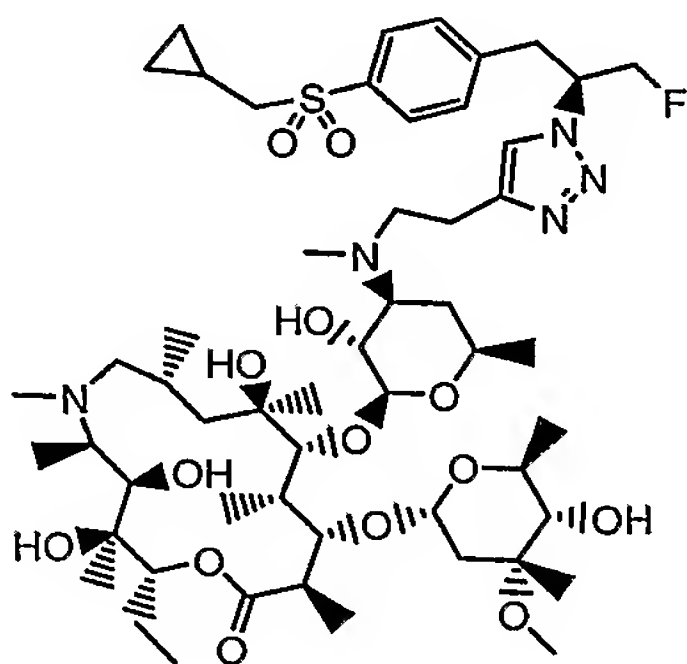
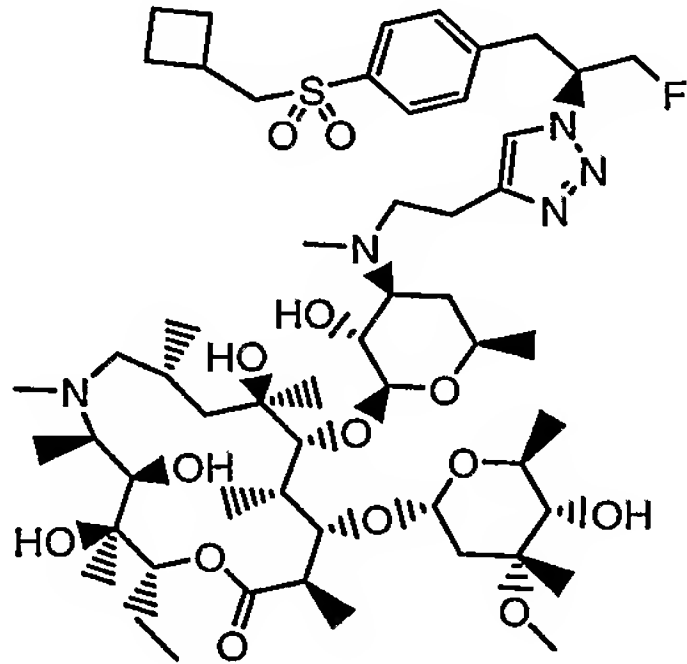
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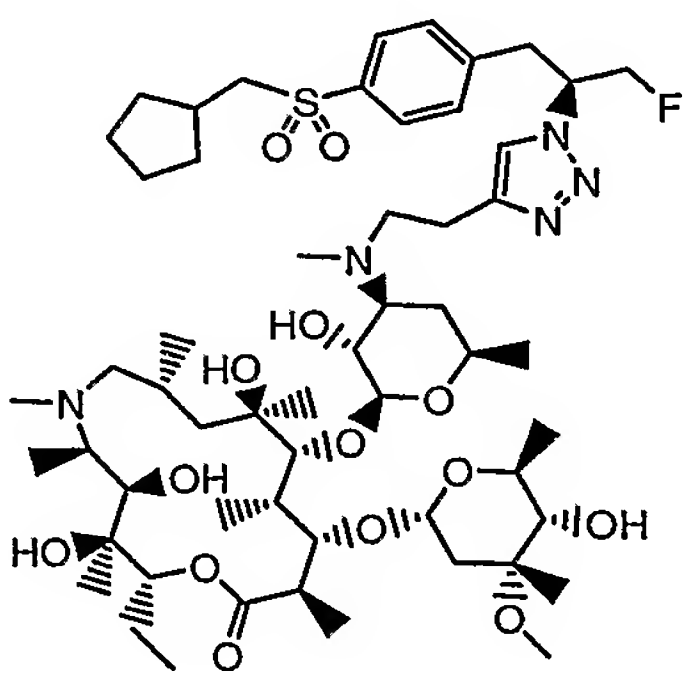
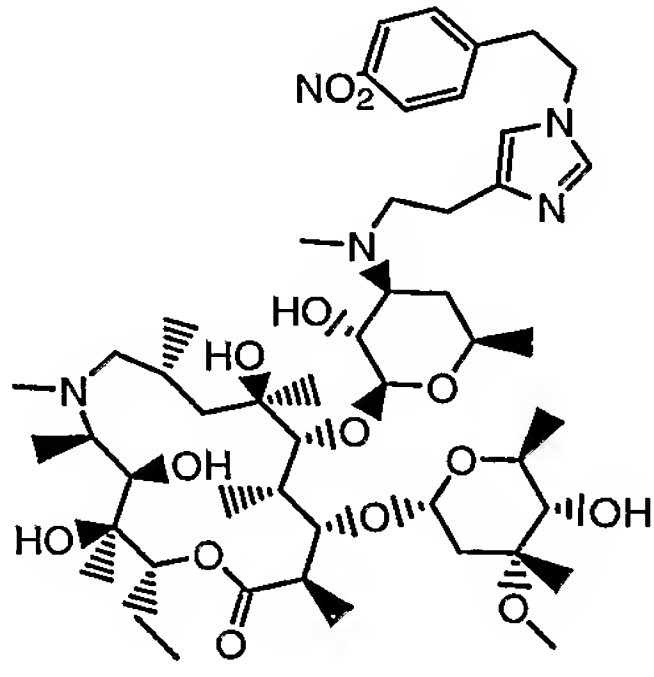
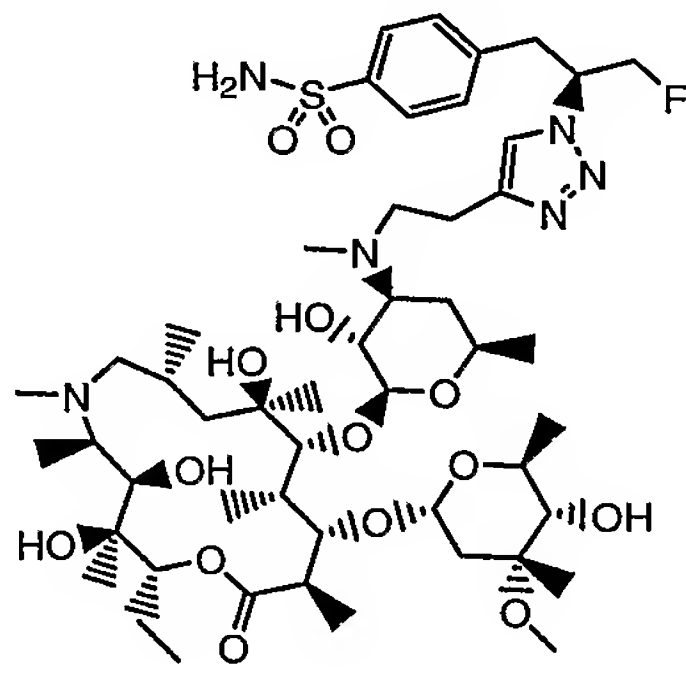
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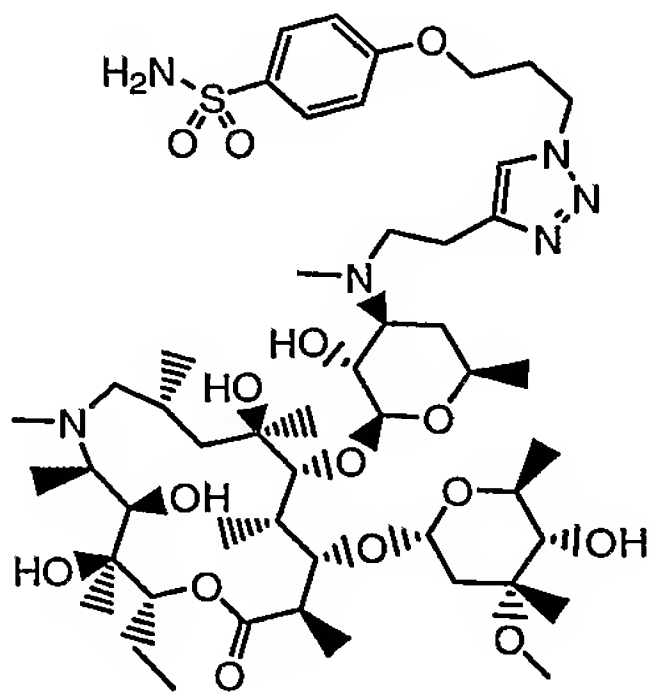
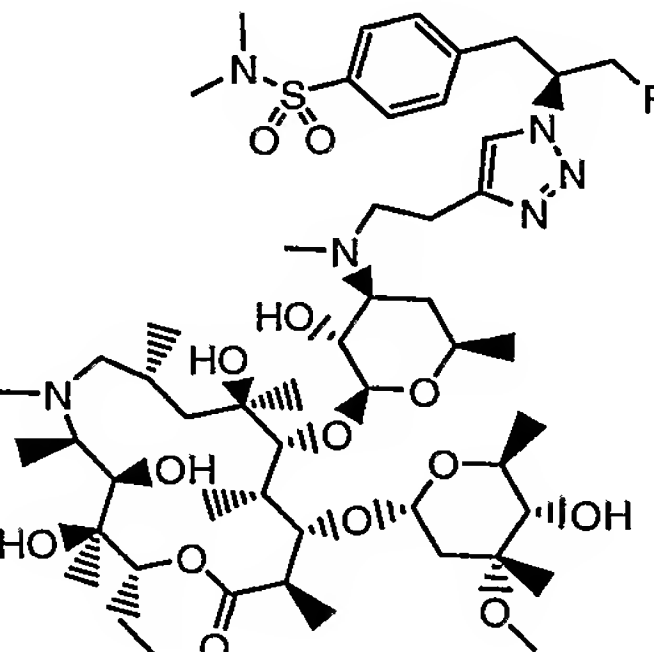
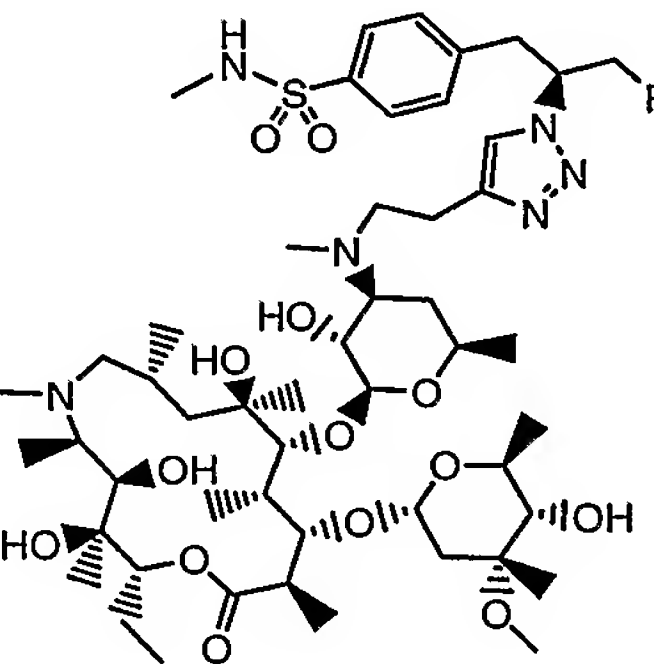
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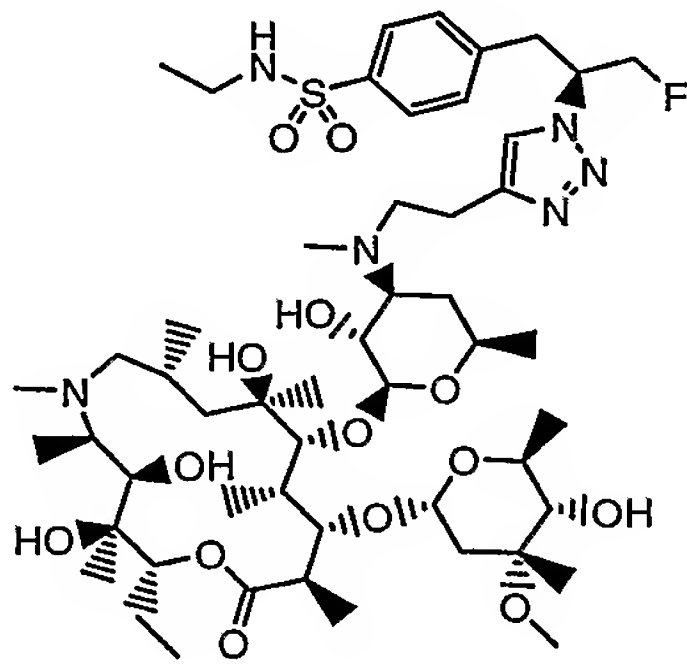
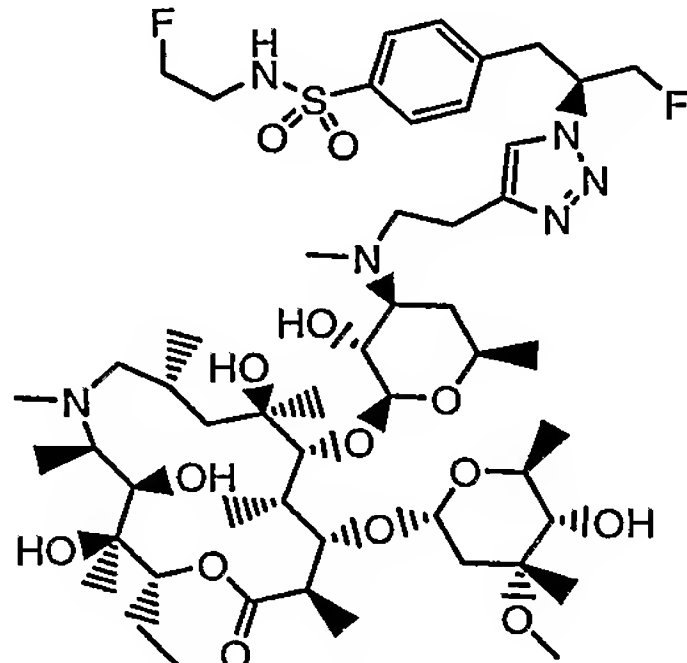
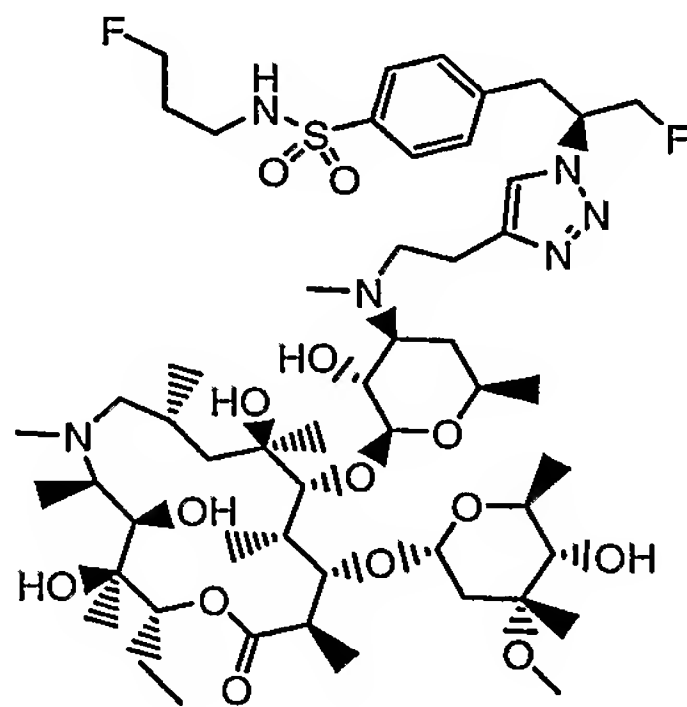
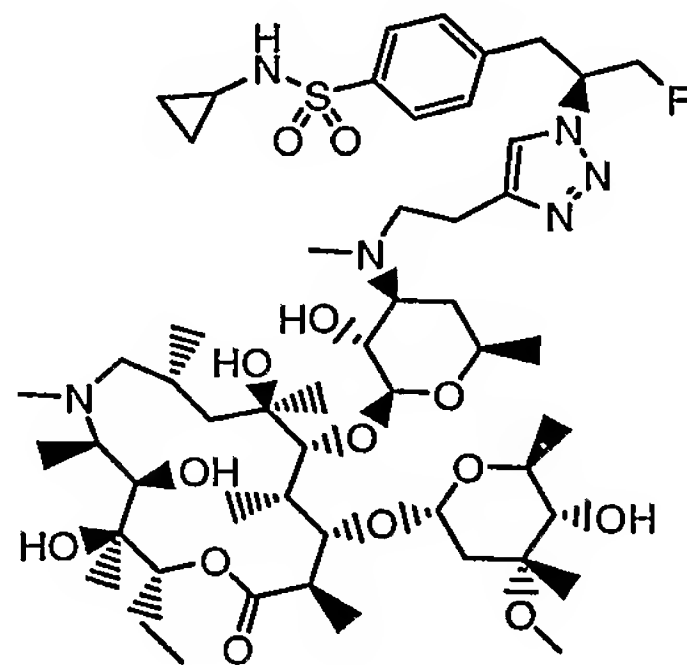
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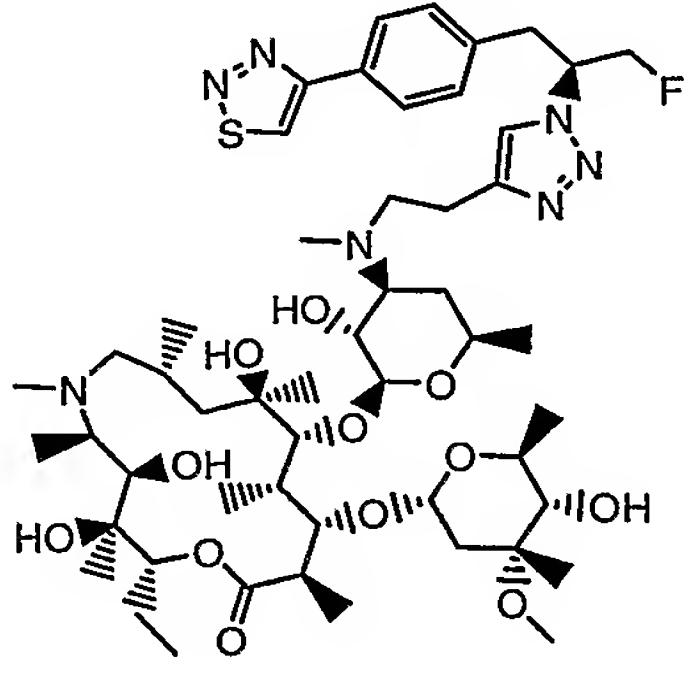
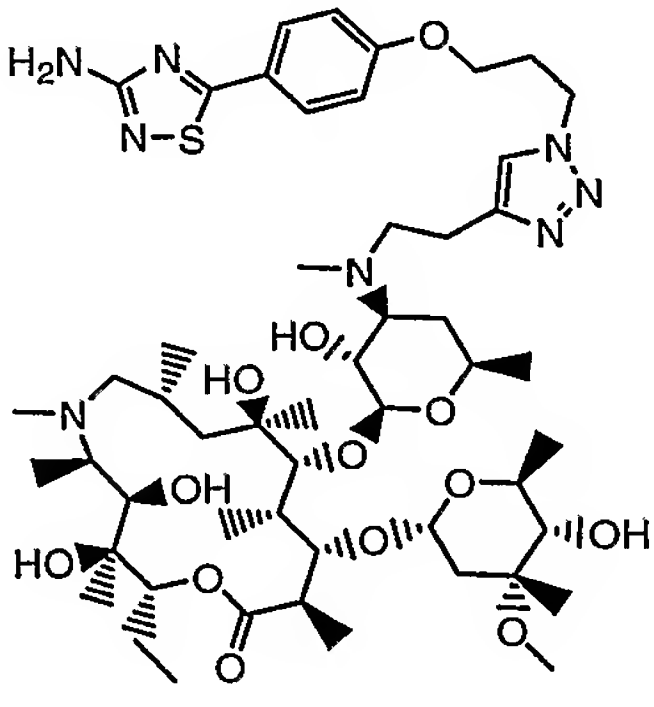
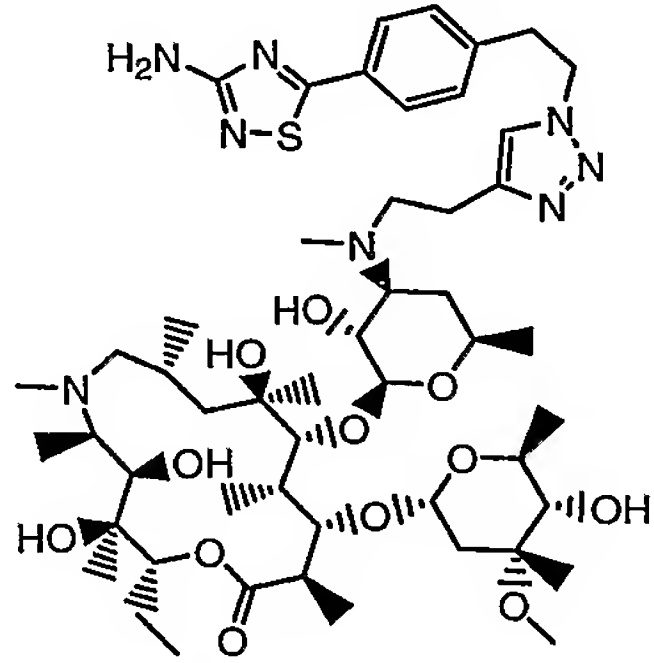
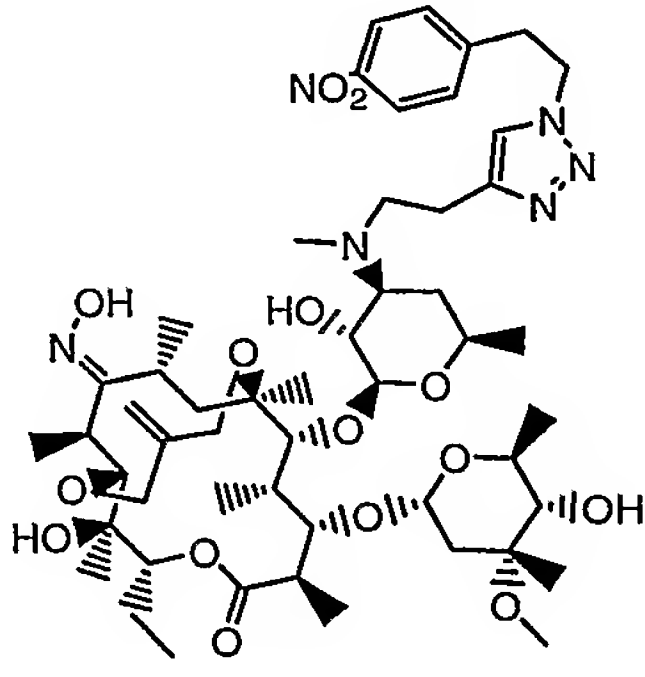
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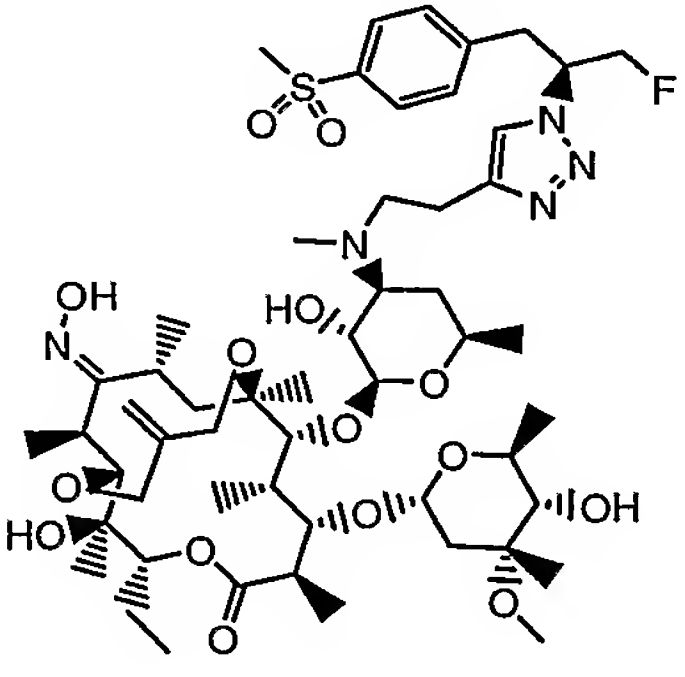
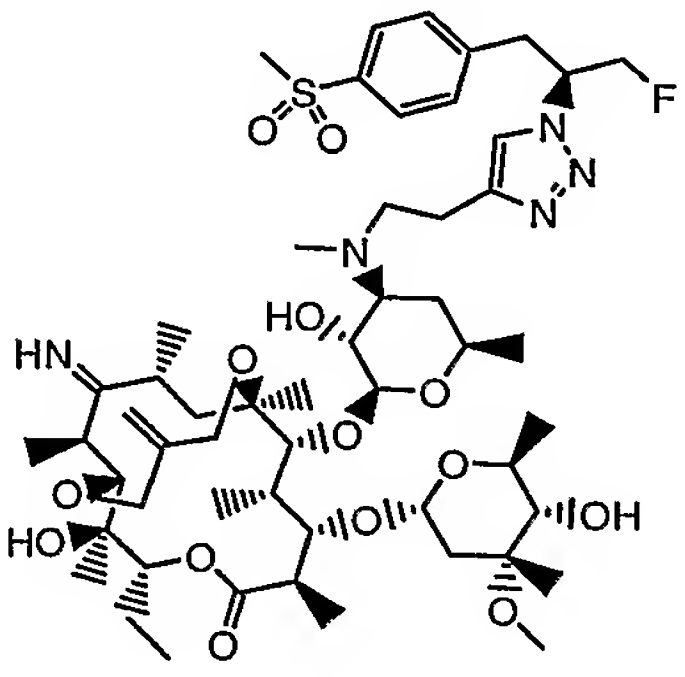
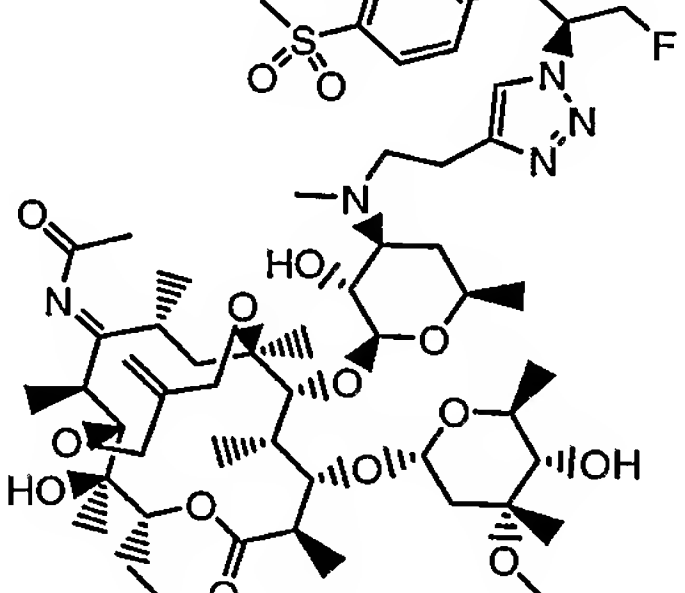
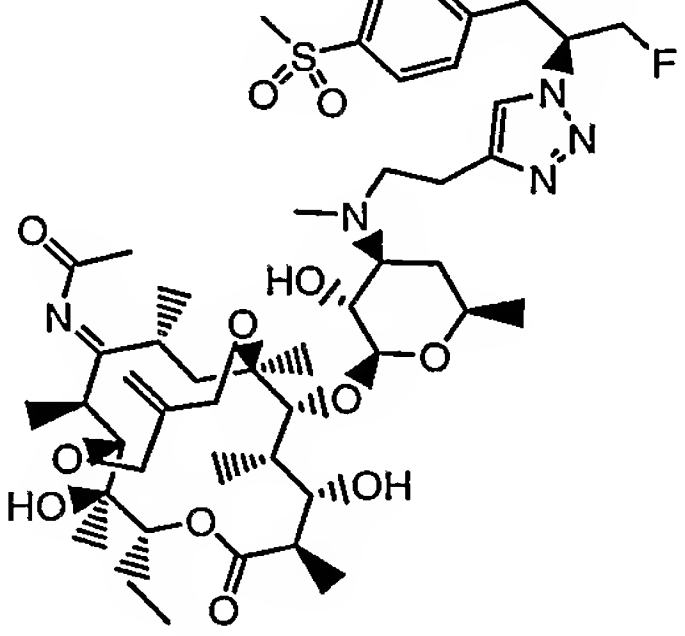
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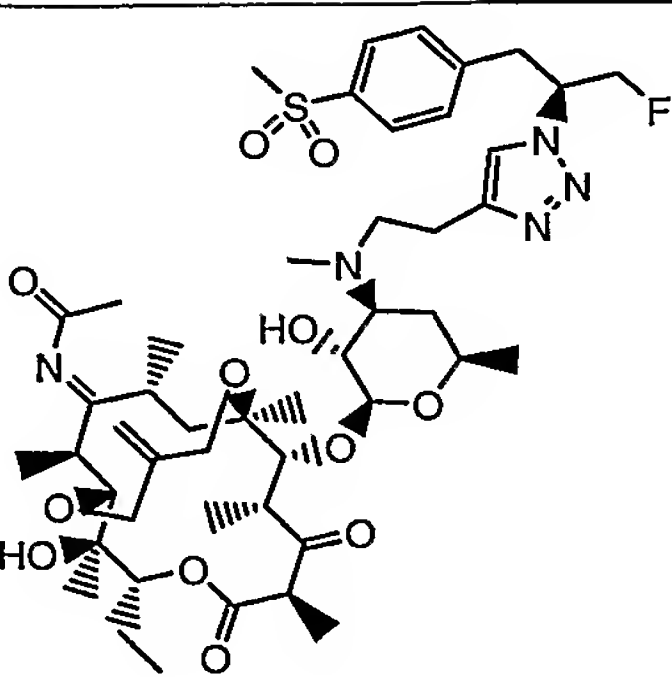
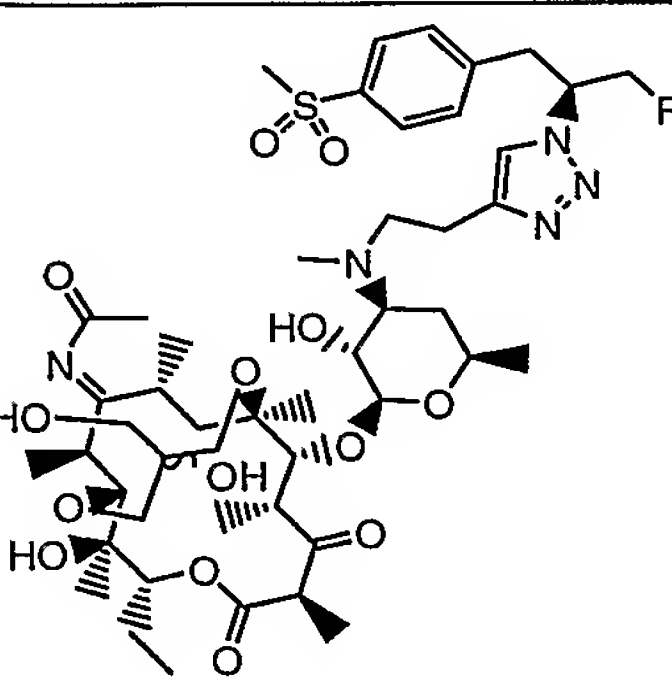
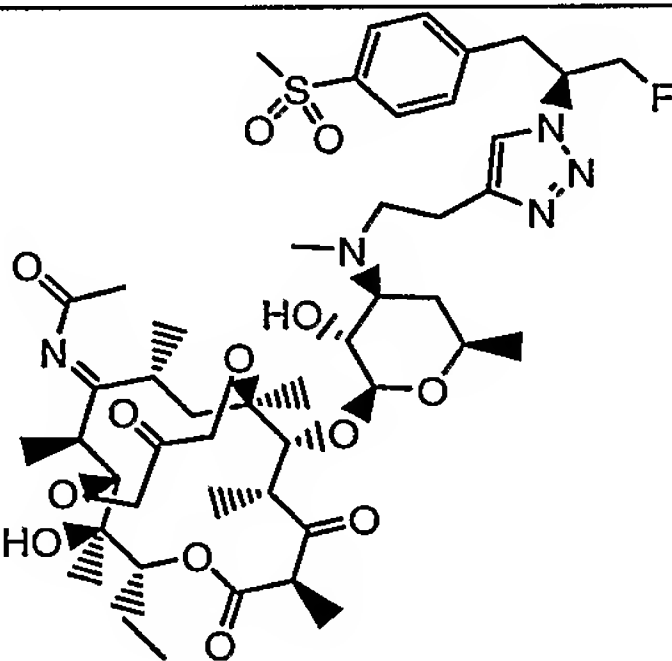
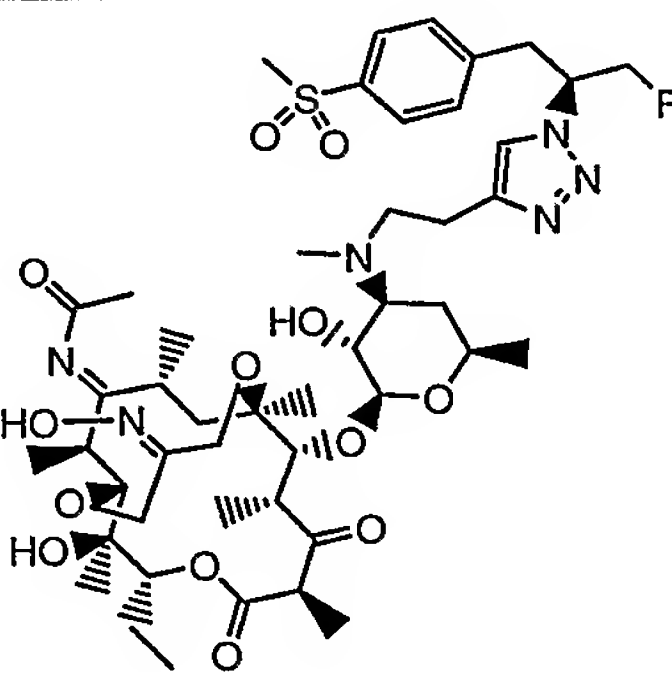
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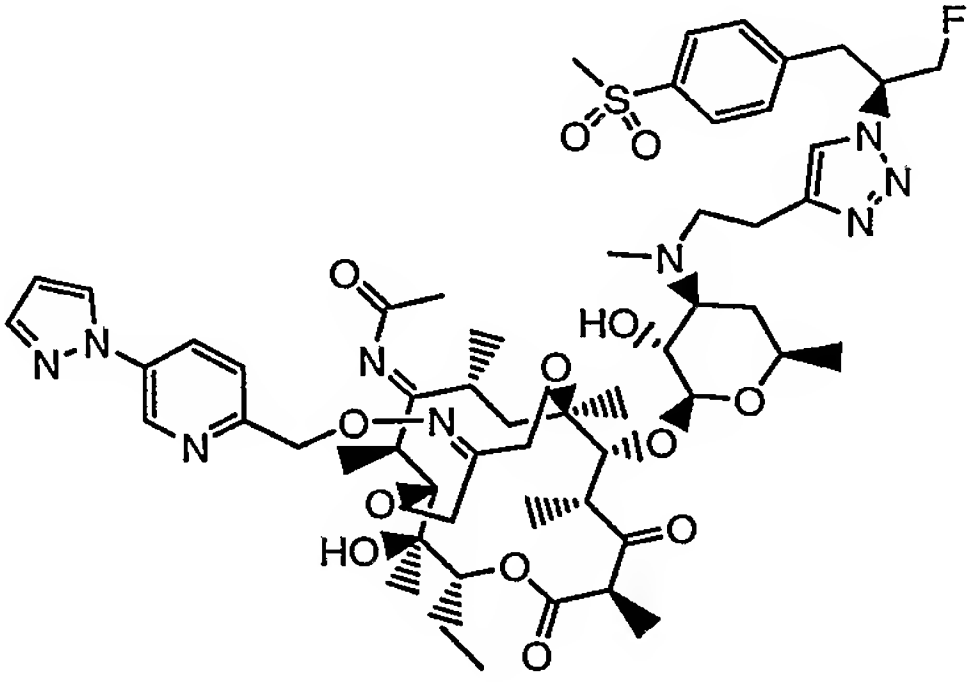
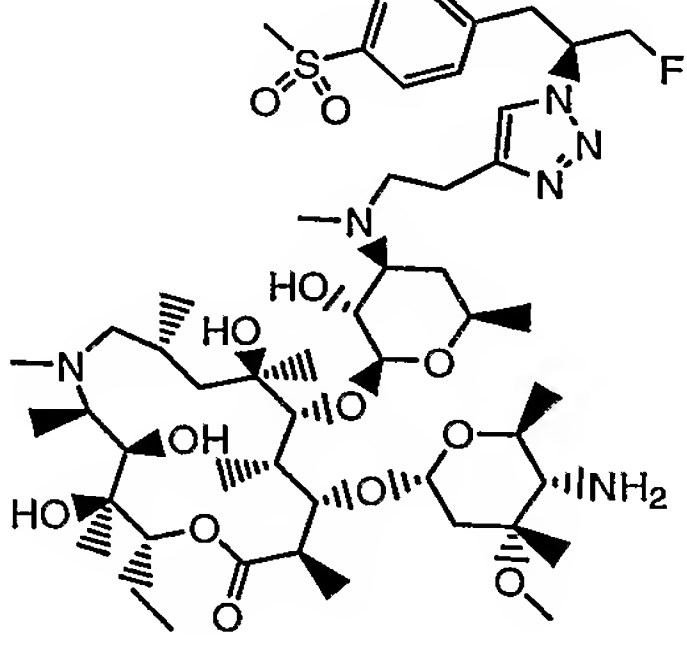
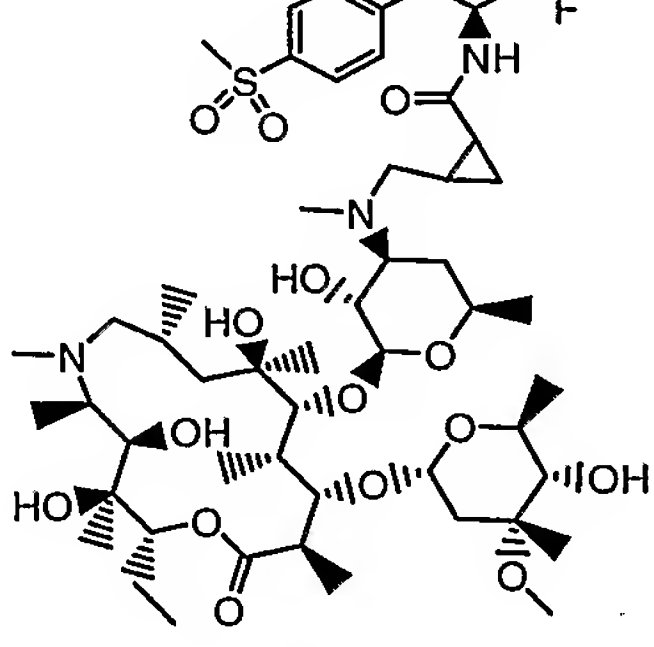
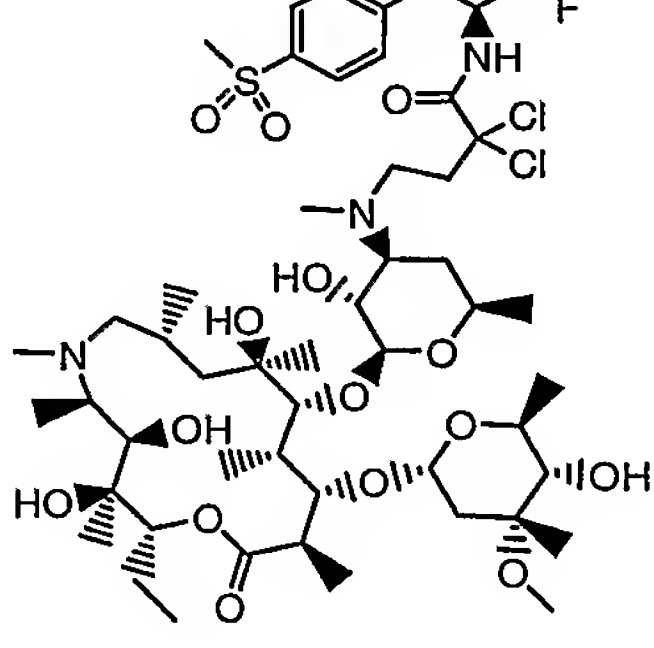
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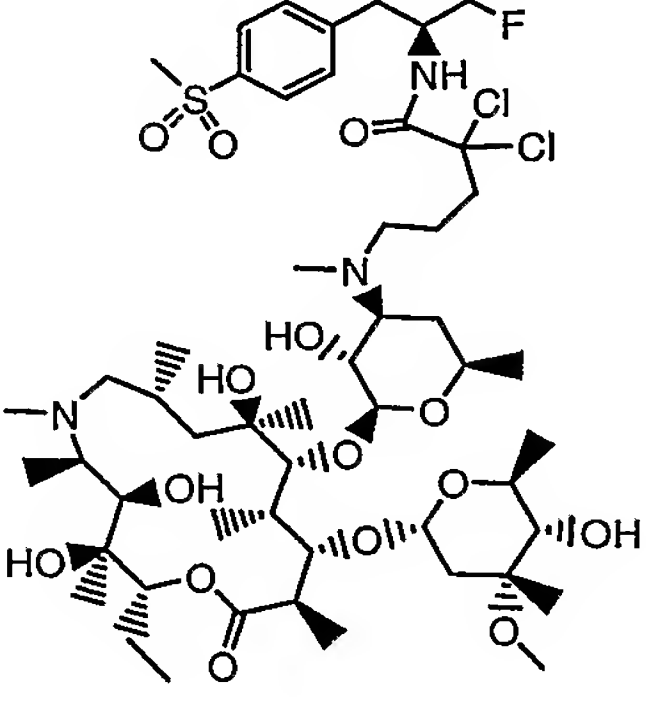
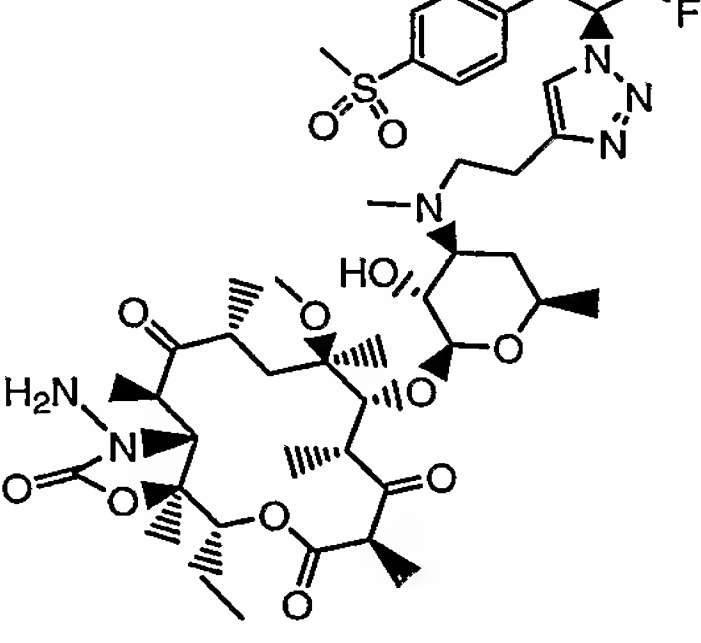
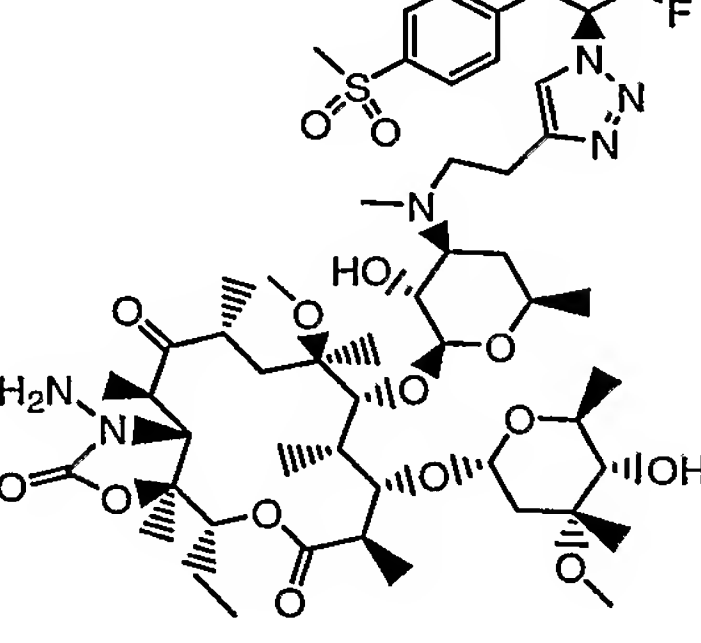
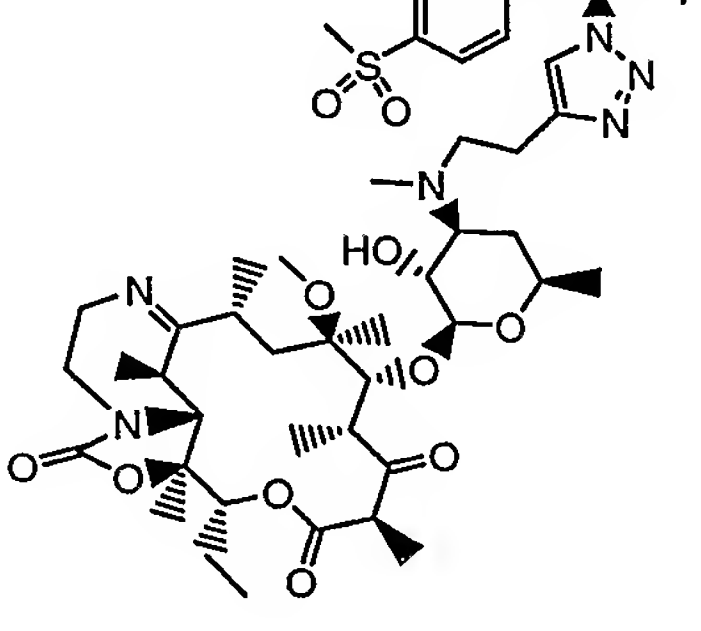
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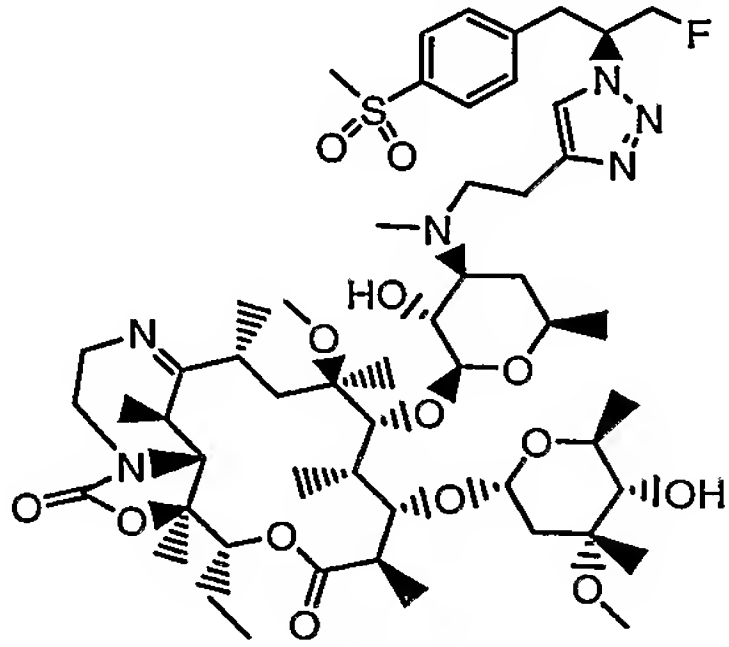
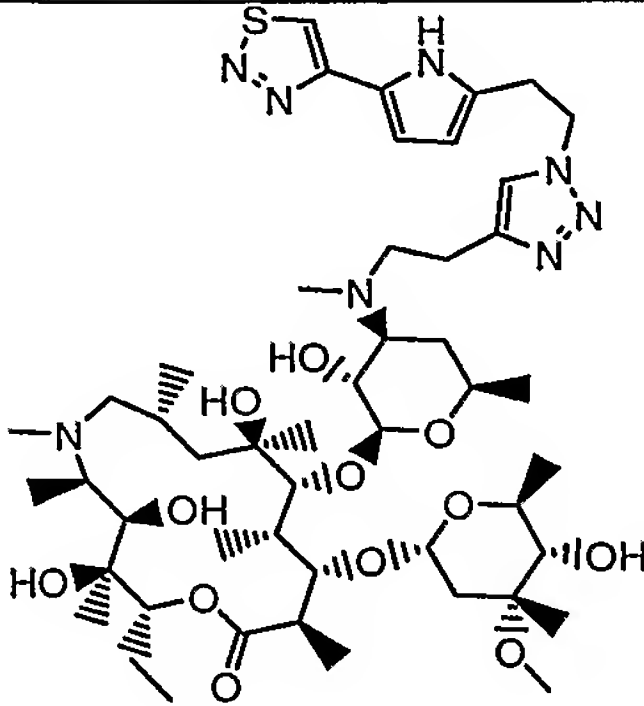
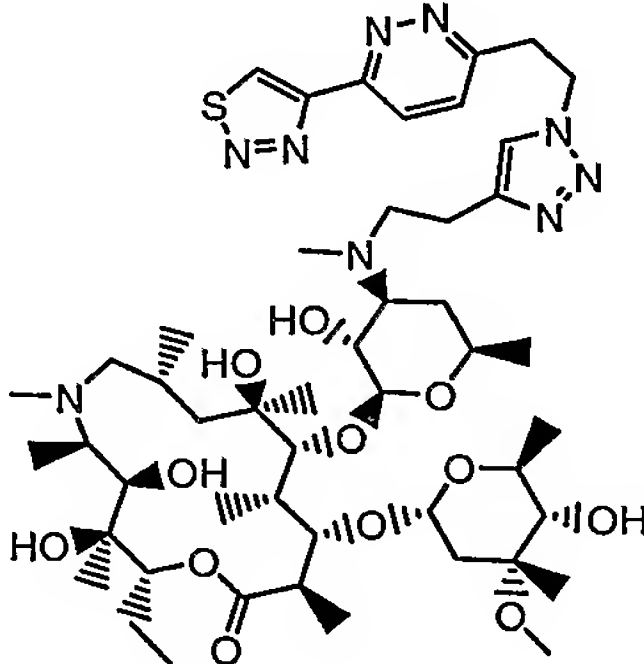
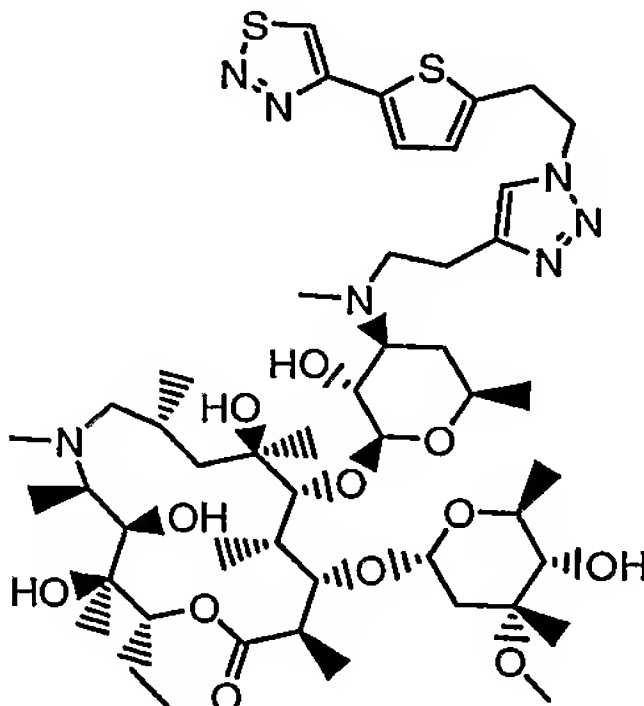
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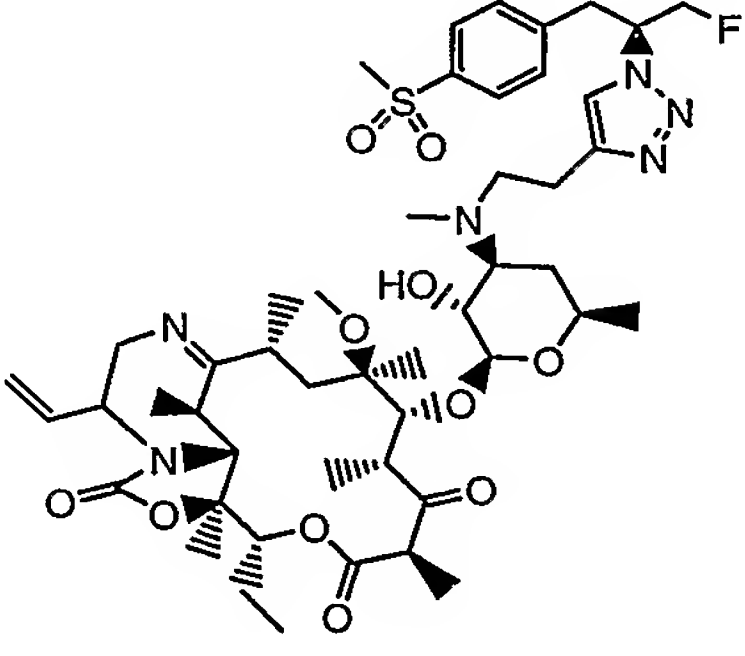
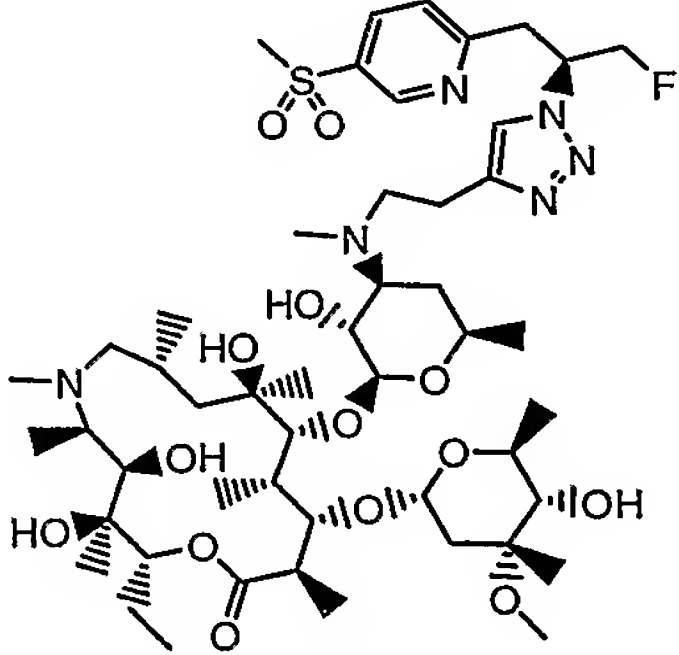
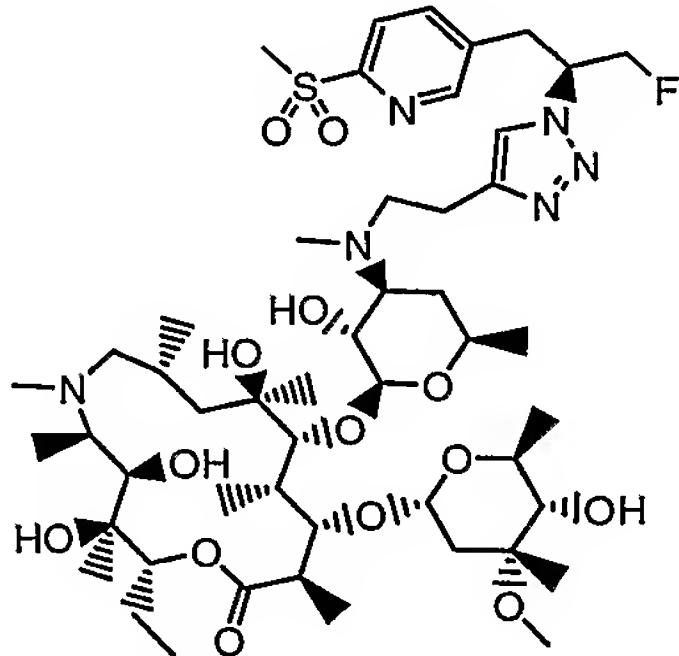
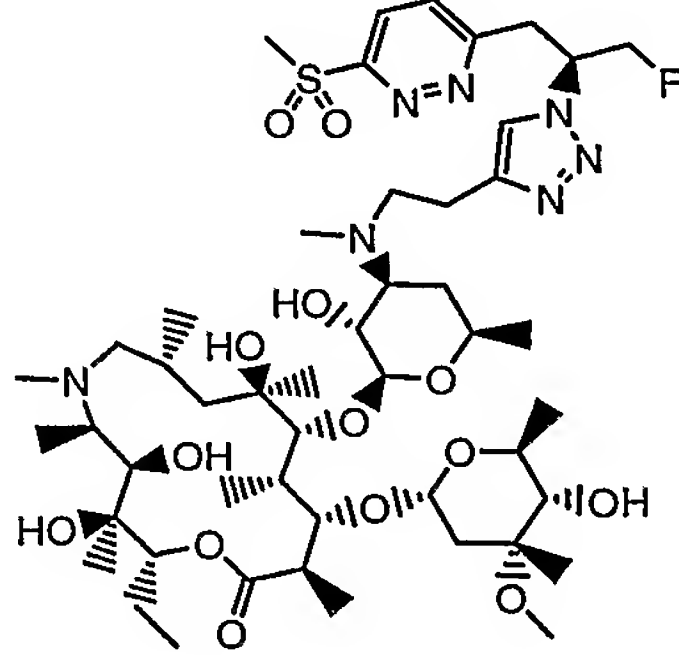
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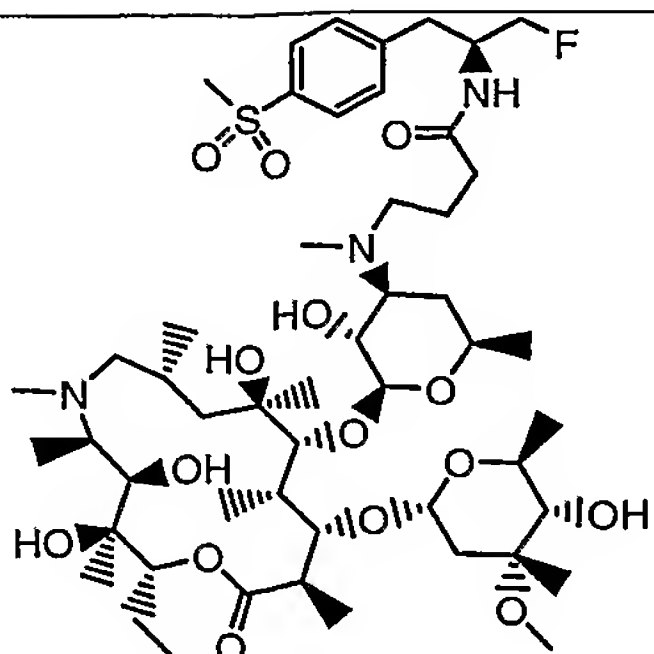
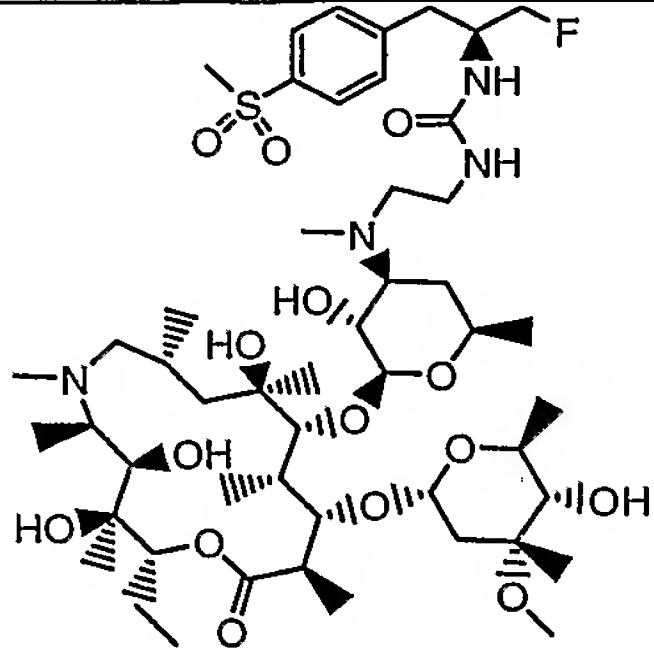
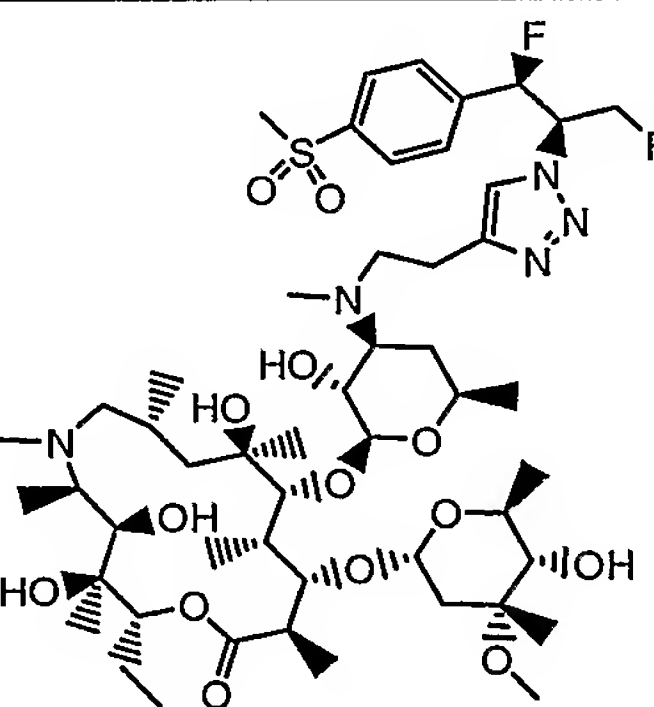
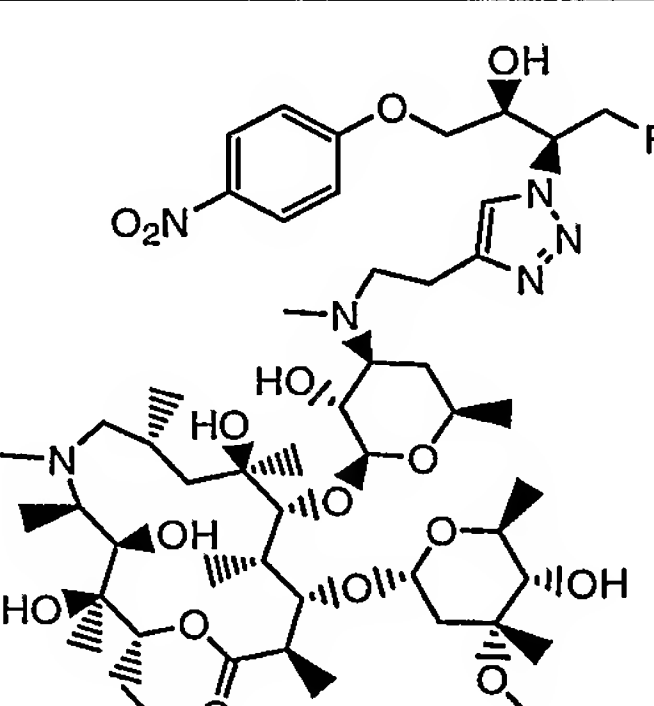
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INCORPORATION BY REFERENCE

The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

5 The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to
10 be embraced therein.